Liraglutide 3.0 mg
Treatment for Weight Management

FDA Advisory Committee Presentation

September 11, 2014

Introduction

Robert Clark

Vice President

Regulatory Affairs

Novo Nordisk

Liraglutide 3.0 mg, Important Treatment Option for Patients

Obesity

- Serious, complex, chronic disease
- Increases risk for other diseases
- More options needed

Liraglutide 3.0 mg

- New, effective weight loss treatment
- Distinct MoA broadens treatment options

Liraglutide is a GLP-1 Receptor Agonist

- Glucagon-like peptide (GLP-1) receptor agonist
- Administered once daily
- Subcutaneously in a pen device

Regulatory History of Liraglutide

- In 2010, liraglutide 1.2 and 1.8 mg approved for treatment of patients with T2DM (Victoza®)
- > 3.3 million patient years of exposure worldwide
- Patients with T2DM achieved some weight loss on liraglutide
- Comprehensive clinical program conducted for liraglutide 3.0 mg for weight management

Proposed Indication for Liraglutide 3.0 mg

- Adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adult patients with an initial BMI of
  - ≥ 30 kg/m^2 or
  - ≥ 27 kg/m^2 with at least one weight related comorbidity
    - Hypertension, dysglycemia (pre-diabetes and type 2 diabetes mellitus), dyslipidemia or obstructive sleep apnea

Significant, Clinically Meaningful, Sustained Weight Loss

- Liraglutide 3.0 mg met FDA benchmarks for weight loss drugs
- Measurable improvements in
  - Weight-related co-morbid conditions
  - Cardiometabolic parameters
  - QoL measures
- Well-described safety profile

Agenda

Need for Additional Pharmacotherapies	**Donna Ryan, MD, FACP** Professor Emerita Pennington Biomedical Research Center
Liraglutide Design and Mechanism of Action in Obesity	**Lotte Bjerre Knudsen, DMSc** Senior Principal Scientist, Novo Nordisk
Dosing Rationale and Efficacy	**Anne Phillips, MD** Senior Vice President, Novo Nordisk
Safety	**Alan Moses, MD** Senior Vice President, Global Chief Medical Officer, Novo Nordisk
Benefit Risk Summary and Proposed Risk Management Plan	**Anne Phillips, MD** Senior Vice President, Novo Nordisk

External Experts

Professor Emerita Pennington Biomedical Research Center	Donna Ryan, MD, FACP
President and Chief Medical Director, MedSleep Asst. Professor of Psychiatry University of Toronto	Adam Blackman, MD, FRCPC, D.ABSM
Marvelle Koffler Chair in Breast Research Professor of Medicine University of Toronto	Pamela Goodwin, MD, MSc
Medical Director of Interventional Cardiology Professor of Medicine University of Texas Southwestern	Steven Marso, MD
Director, Pancreatitis Center Medical Director, Pancreatic Islet Autotransplantation Program Division of Gastroenterology, Johns Hopkins Hospital	Vikesh Singh, MD, MSc

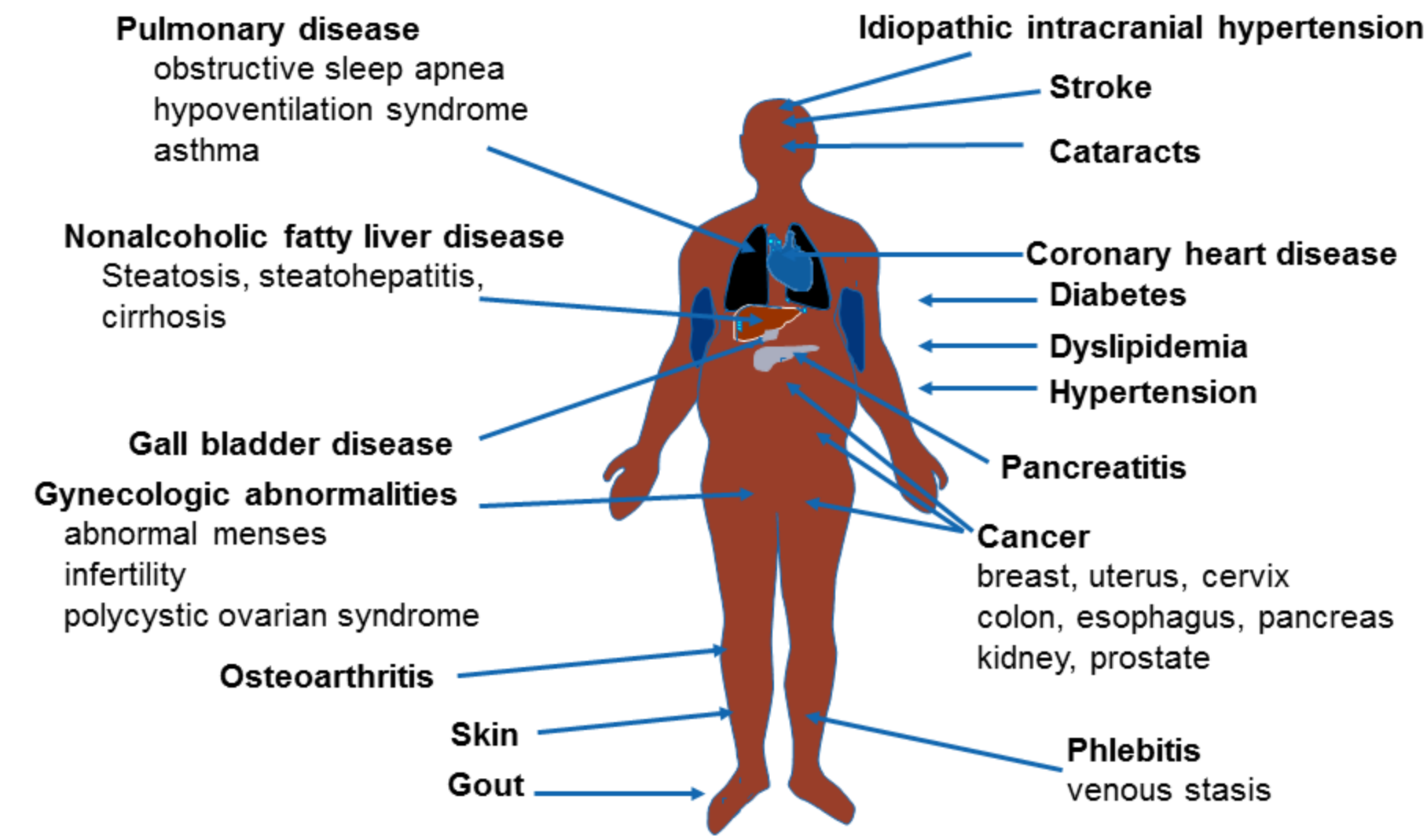
Weight Management as a Pathway to Health Improvement: Need for Additional Pharmacotherapies

Donna Ryan, MD, FACP

Professor Emerita

Pennington Biomedical Research Center

Obesity Produces Morbidity and Affects How Patients Feel and Function



Goals of Obesity Management

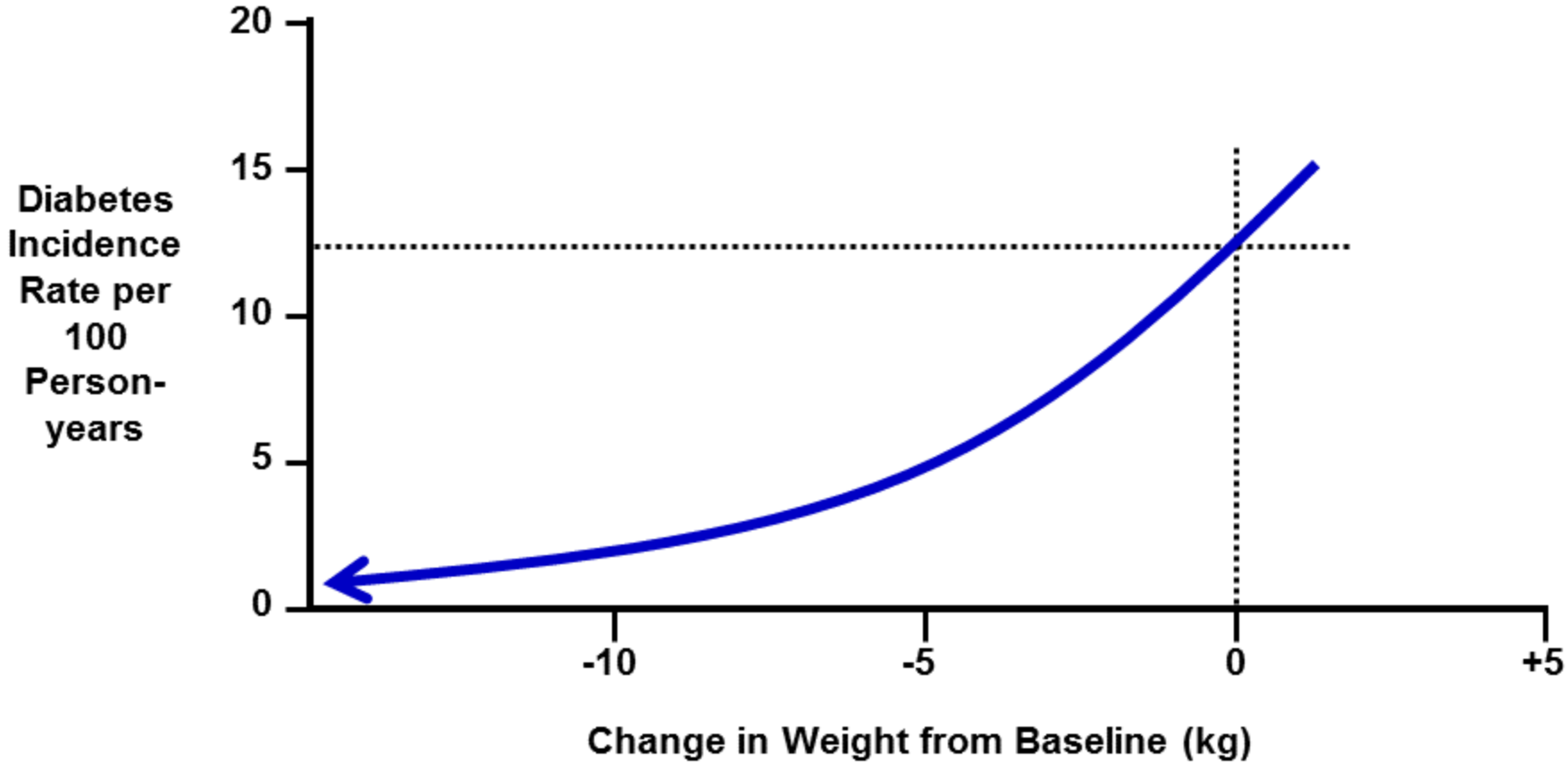
- Sustained weight loss is the primary goal
- Provide clinically meaningful medical benefits
  - Improve markers of cardiovascular risk
  - Improve how patients feel
  - Reduce functional impairment

Health Improvements Are Observed with Weight Loss

- 2013 Guidelines (NHLBI, AHA/ACC/TOS)
  - 5-10% weight loss goal[1]
- FDA Guidance
  - 5% weight loss clinically meaningful
- Greater weight loss associated with greater health improvements

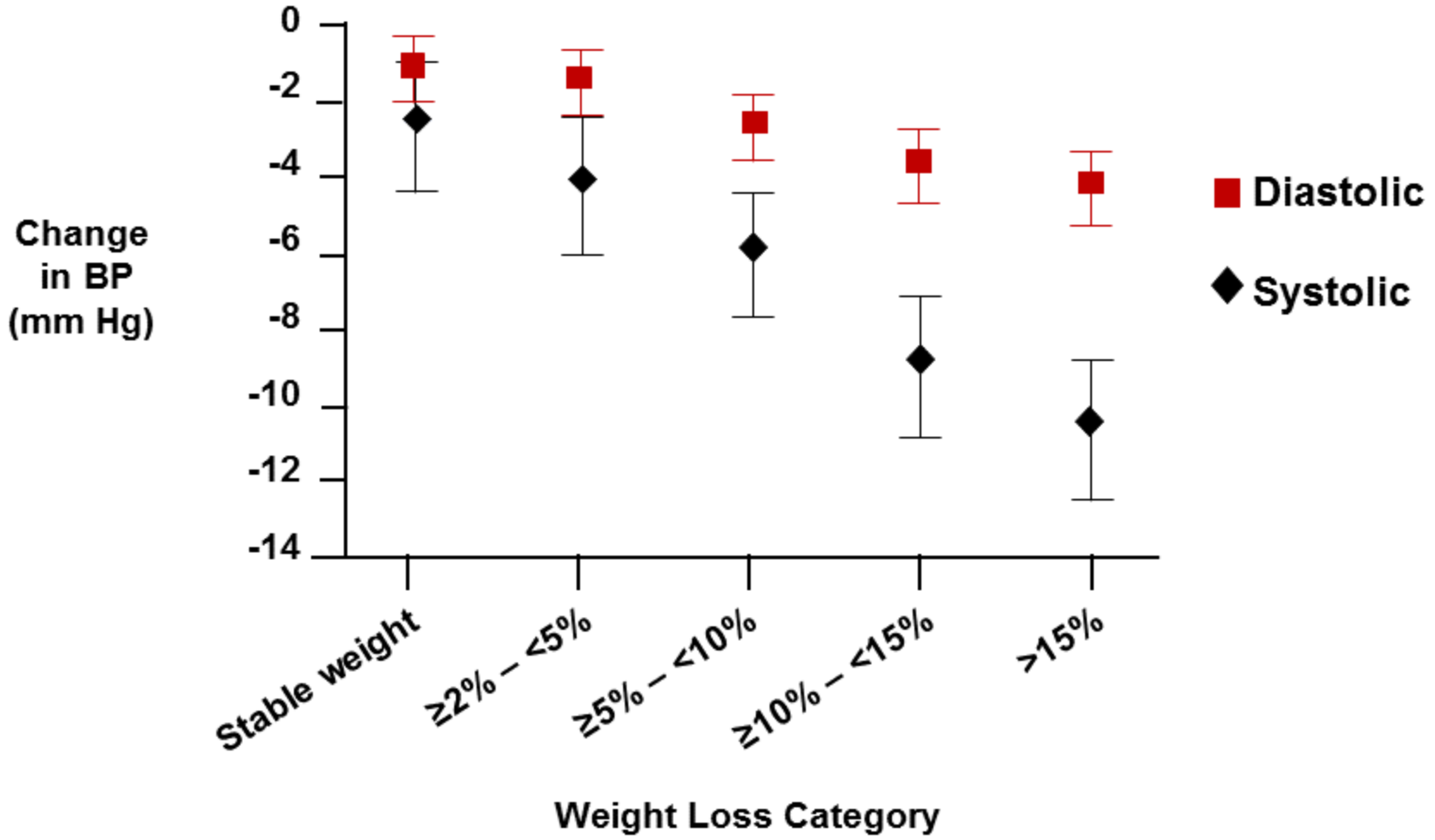
1. No Authors Listed; 2013; *Obesity* doi: 10.1002/oby.20660. [Epub ahead of print]
1. Jensen et al. 2013; *JACC* doi: 10.1016/j.jacc.2013.11.004. [Epub ahead of print]
1. Jensen et al., 2013; *Circulation* [Epub ahead of print]

The DPP Experience: Every Kilogram Lost Reduced Risk of Diabetes



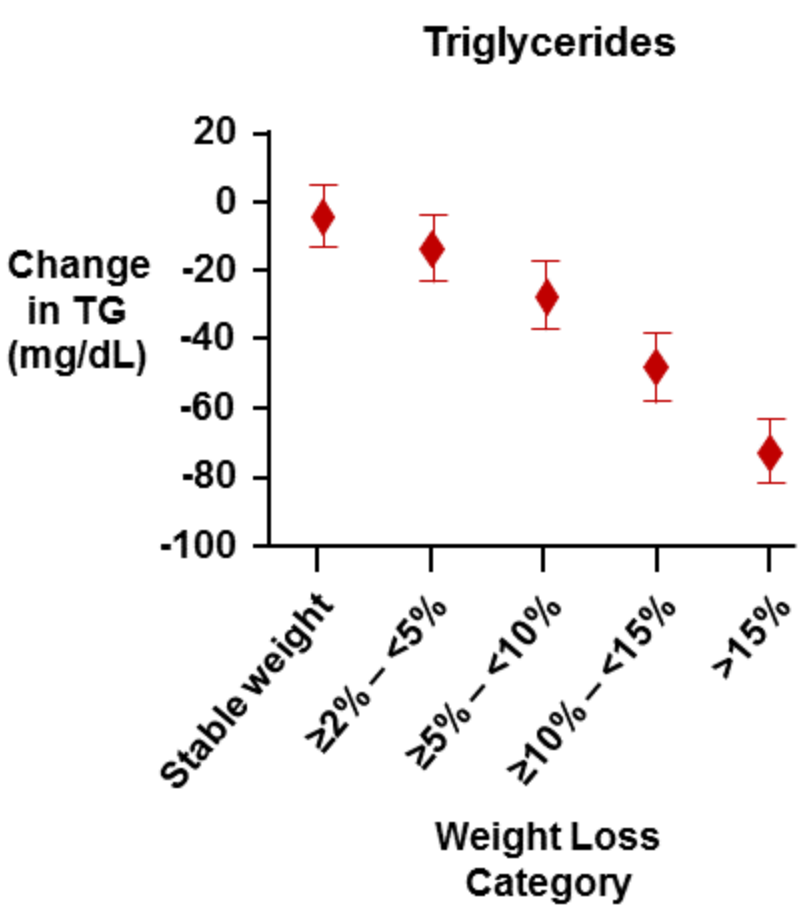
Adapted from Hamman et al., *Diabetes Care (2006)* 29: 2102-2107.

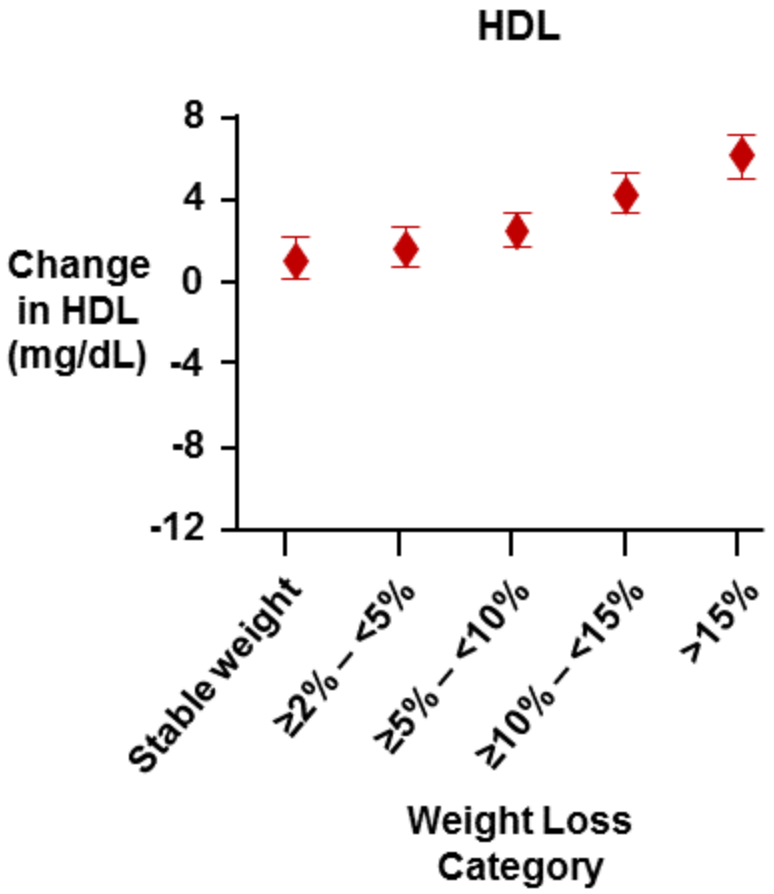
Look AHEAD 1-year Data: More Weight Loss, Lower Blood Pressure



Adjusted LSmean (95% CI). Stable weight defined as ±2% of baseline weight. P<0.0001 vs baseline for all weight categories.
Wing RR et al. *Diabetes Care* (2011) 34(7):1481-1486.

Look AHEAD: More Weight Loss Improves CVD Markers





Adjusted LSmean (95% CI). Stable weight defined as ±2% of baseline weight. P<0.0001 vs baseline for all weight categories.
Wing RR et al. *Diabetes Care* (2011) 34(7):1481-1486.

Complex Factors Inhibit Weight Loss

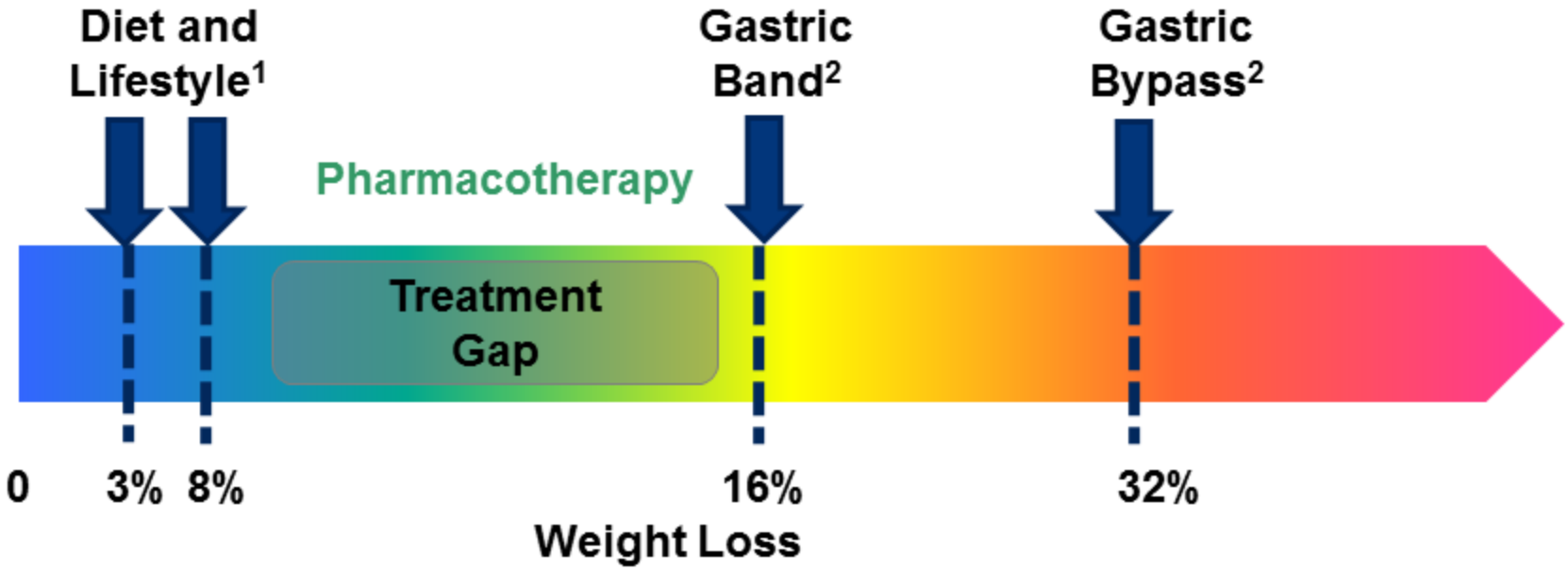
- Life events, stress, and genetic risks
- Physiological resistance to weight loss
  - Increased hunger, decreased satiety after weight loss[1]
  - Metabolic adaptation[2]
    - Decreased resting energy expenditure
    - Creates handicap to lose weight

1. Sumithran et al., *NEJM* 2011; 365(17): 1597-604
2. Schwartz et al., *Obes Rev* 2010; 11(7): 531-547

Complex Chronic Diseases Require Multiple Treatment Options

- No one treatment works for all
- Multiple drugs available for most chronic diseases
  - > 100 hypertension medications
  - > 40 T2DM medications
- Only 3 drugs for chronic weight management

Treatment Gap in the Management of Patients With Obesity



1. Jensen et al., *Circulation*. Published Online Nov 12, 2013.
2. Courcoulas et al. *JAMA* (2013) 310(22):2416-2425

Summary: We Need More Treatment Options for Obesity

- Serious disease that increases risks for other diseases
- Weight loss produces clinically meaningful health improvements
- More health benefits with more weight loss
- Difficult to lose and sustain weight loss

Liraglutide Design and Mechanism of Action in Obesity

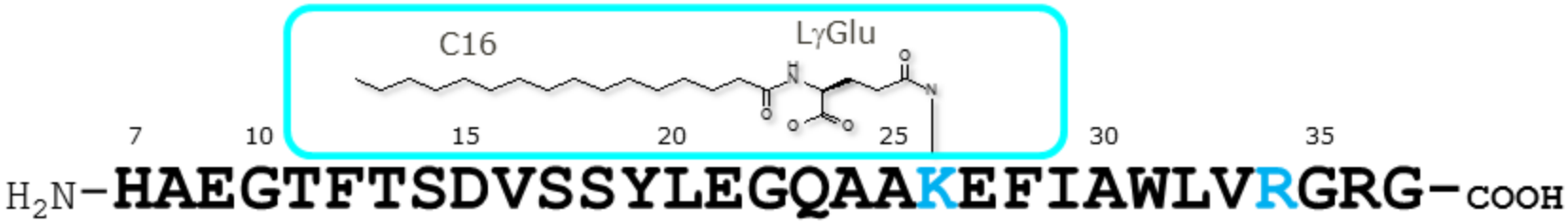
Lotte Bjerre Knudsen, DMSc
Senior Principal Scientist
Diabetes Research Unit
Novo Nordisk

Overview

- Rationale for liraglutide molecule
  - Design of liraglutide molecule
  - GLP-1 receptor role in appetite regulation
- Mechanism of action for weight loss
  - Physiology
  - Distinct from other pharmacotherapies

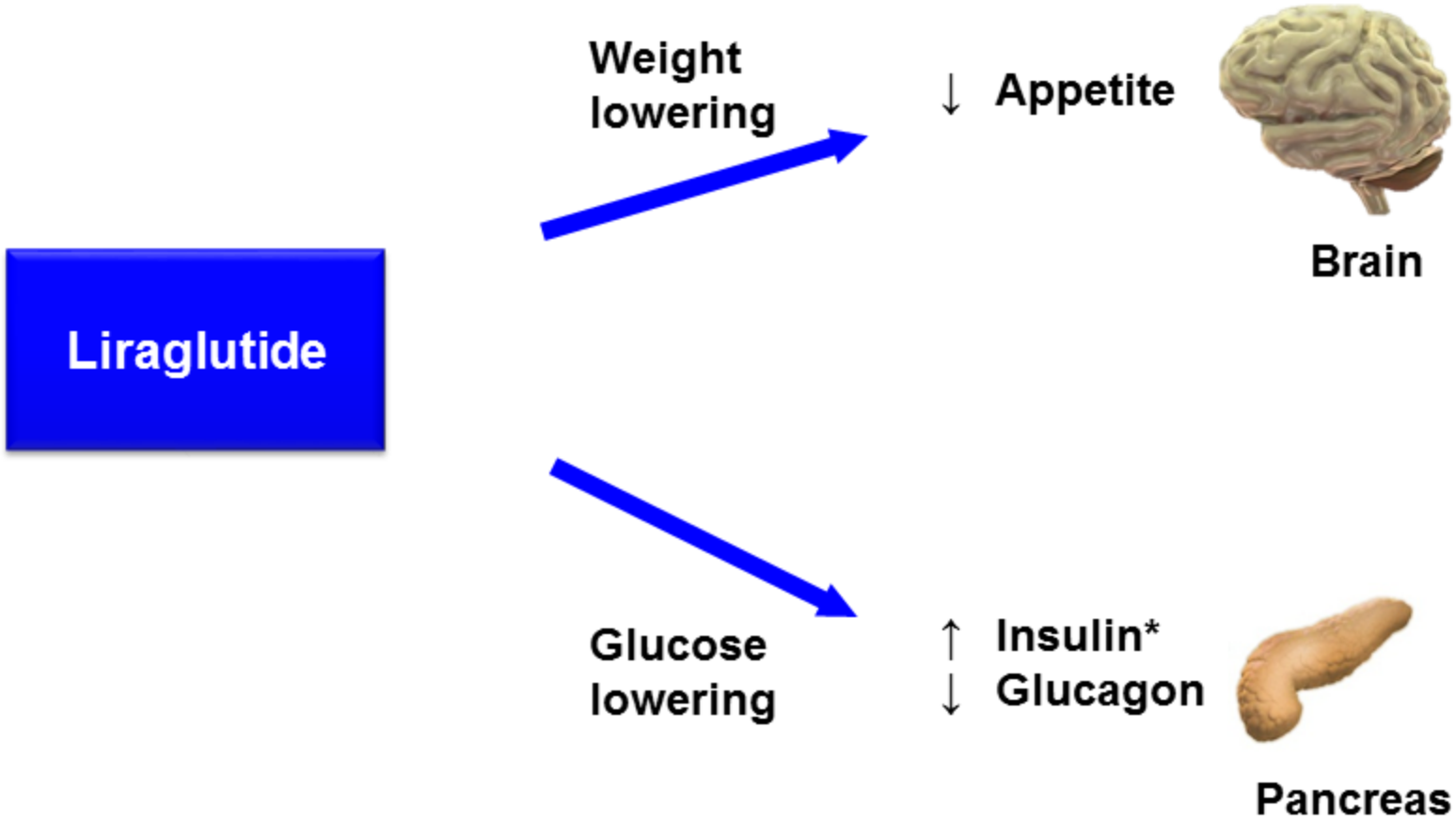
Liraglutide Pharmacology

- Acts through specific G-Protein Coupled Receptor
- 97% homology to human GLP-1
- Binds to albumin through natural fatty acid
- 13 hour half-life
- Metabolized by peptidases



Knudsen LB et al., J Med Chem 2000; 43(9):1664-1669

Liraglutide - Independent Effects on Glucose and Body Weight



*Insulin secretion is glucose-dependent and occurs only under hyperglycemic conditions

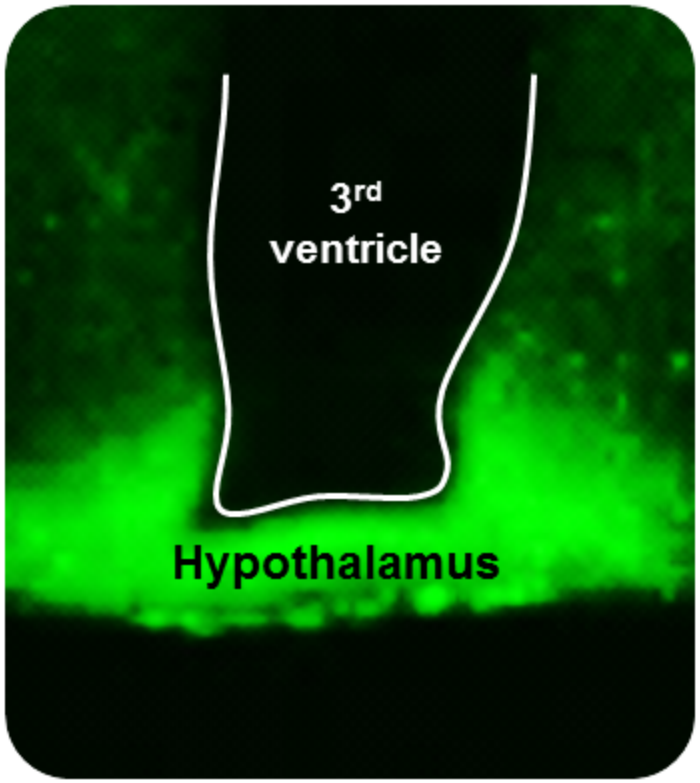
Modified from: Meier JJ, Nat. Rev. Endocrinol. 8 (12): 728-742; 2012

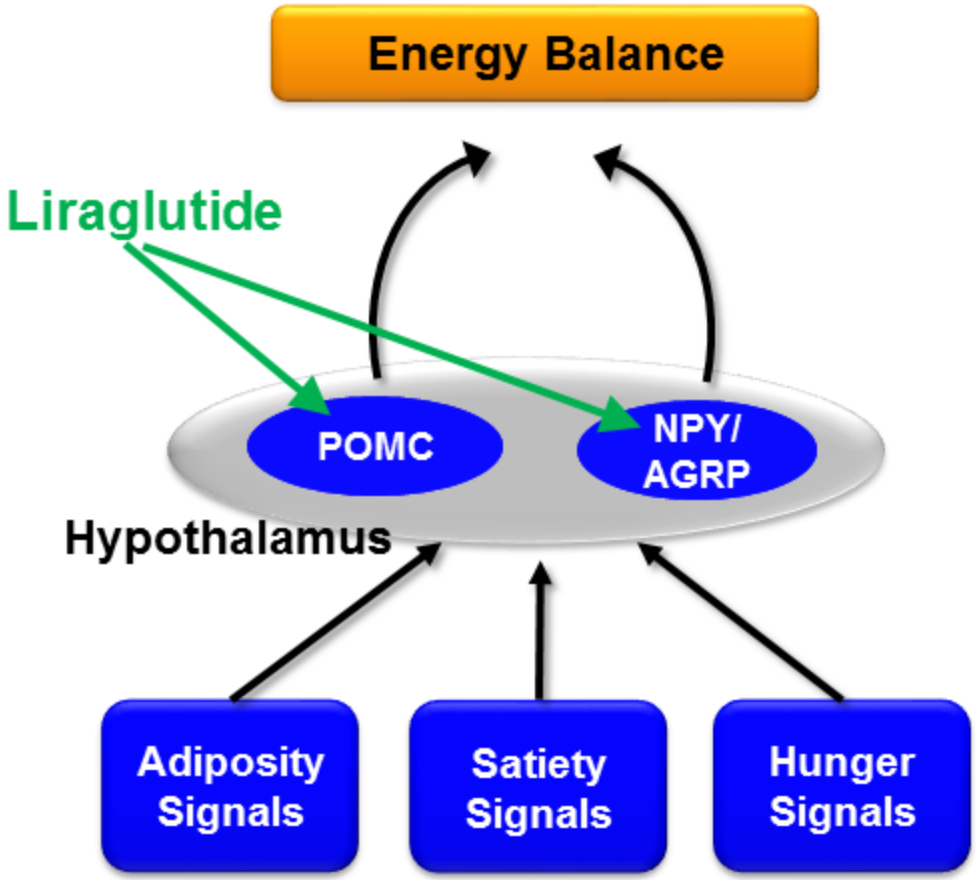
Native GLP-1 – An Important Physiological Regulator of Appetite

- GLP-1R expressed in specific hypothalamic regions
  - Relevant for energy homeostasis
- Lowers energy intake
- Reduces overall appetite
  - Increases feelings of satiety
  - Reduces feelings of hunger
- Does not increase energy expenditure

Turton MD et al., Nature 1996; 379(6560):69-72.
Fint A et al., J Clin Invest 1998; 101(3):515-520.

Liraglutide Works Directly in Brain Areas Associated with Appetite Regulation





POMC, proopiomelanocortin;
NPY, neuropeptide Y; AGRP, agouti-related peptide;

Secher A et al., J. Clin. Invest. 2014; 24(10): doi:10.1172/JCI75276

Liraglutide: Mechanistically Distinct Treatment Option for Obesity

- Based on native GLP-1, a physiological regulator of appetite and glycemia
- Increases satiety and decreases hunger
- Reduces energy intake

Dosing Rationale and Efficacy of Liraglutide 3.0 mg

Anne Phillips, MD

Senior Vice President

Clinical, Medical and Regulatory Affairs

Novo Nordisk

Liraglutide 3.0 mg: Clinically Meaningful, Statistically Significant, Sustained Weight Loss

- All trials met pre-specified primary endpoints
- All trials met at least one FDA benchmark
- Weight loss across all sub-groups
- Weight loss maintained while on therapy
- Improvements in co-morbidities, cardiometabolic parameters and QoL

FDA Efficacy Benchmarks for Weight Loss Drugs

- ≥ 5% difference in mean weight loss between active and placebo; statistically significant

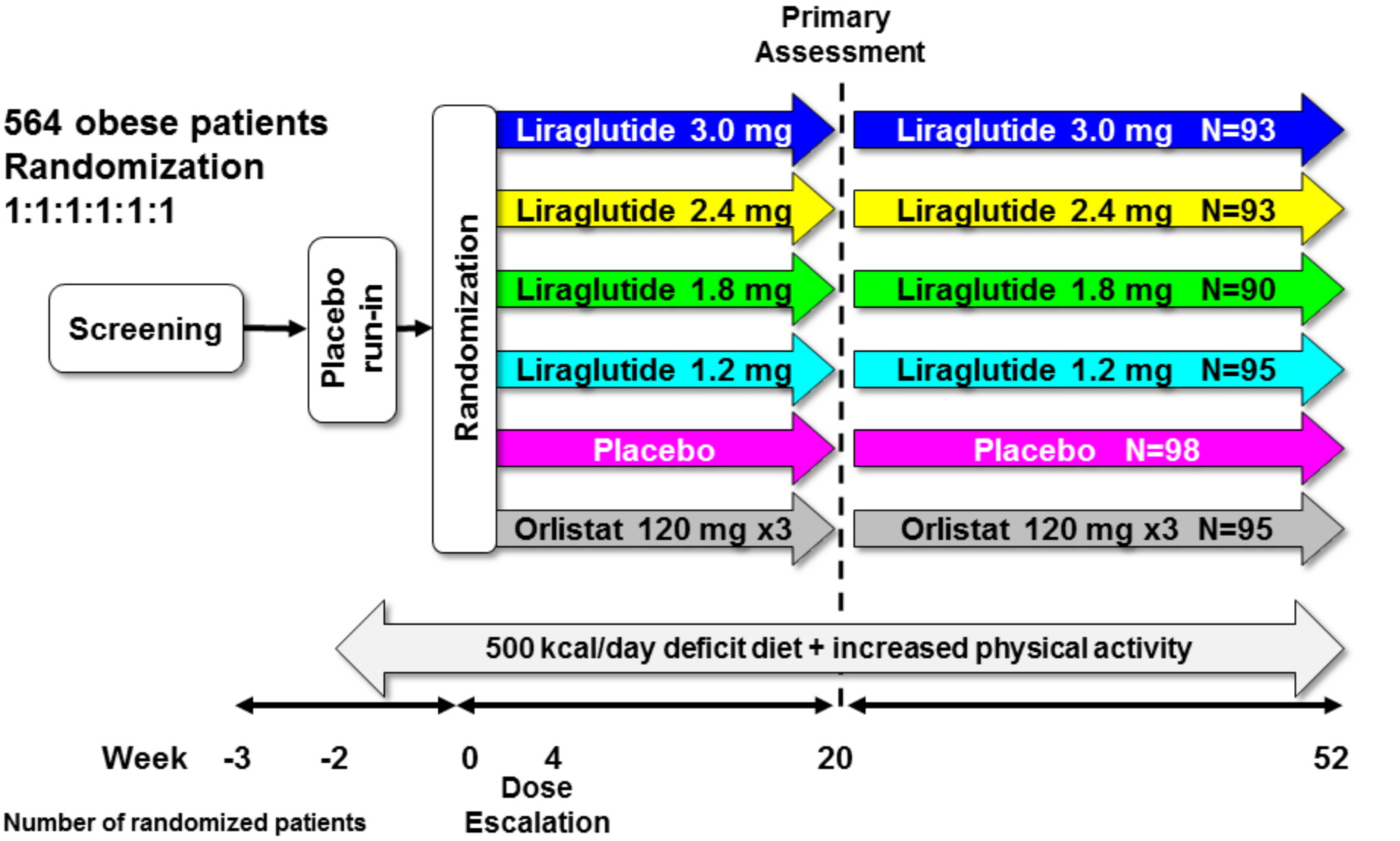
OR

- ≥ 35% in active arm lose ≥ 5% of baseline body weight and; double placebo, statistically significant

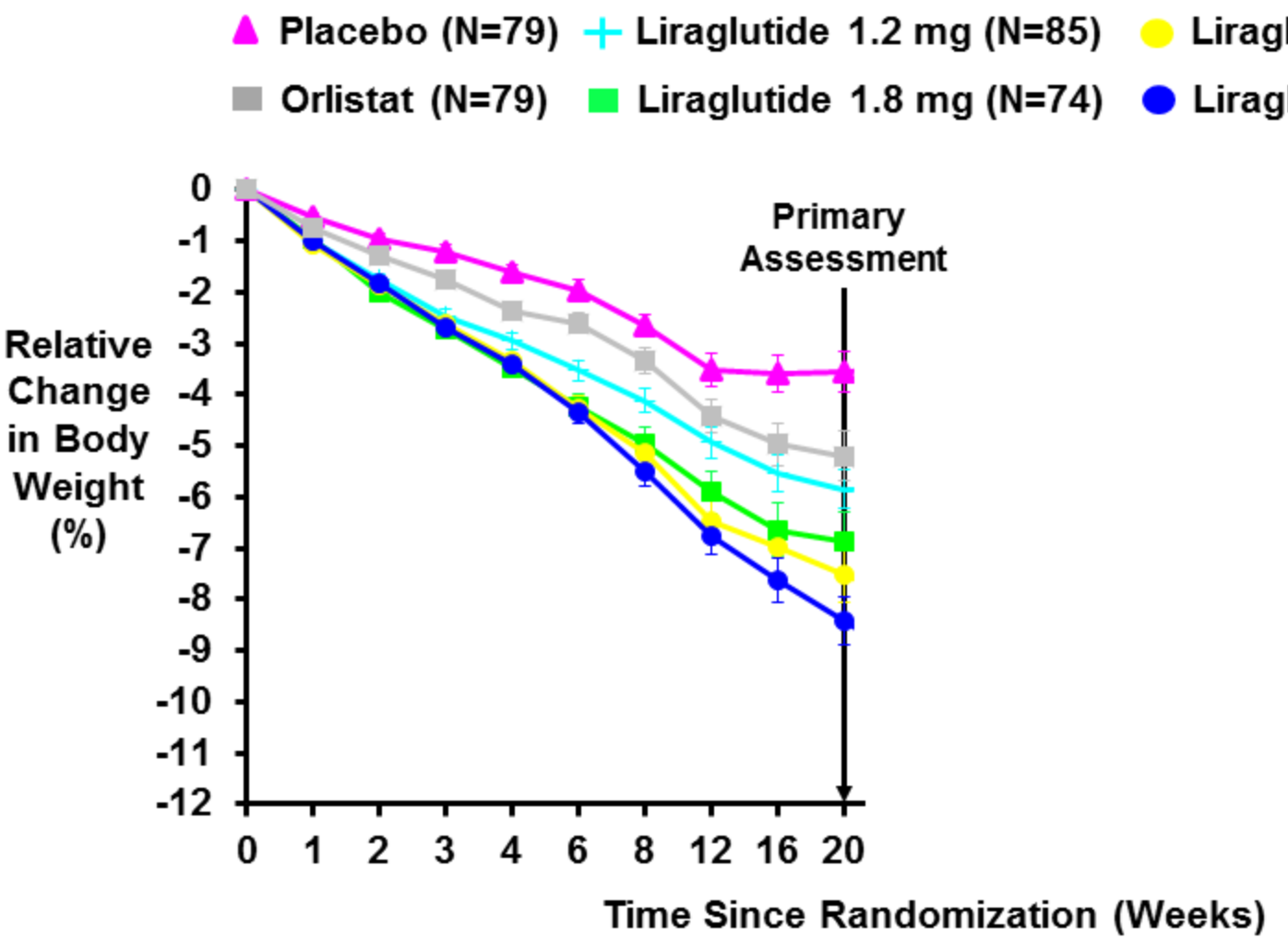
AND

- Improvement in cardiometabolic parameters

Trial 1807 Design: Dose Finding

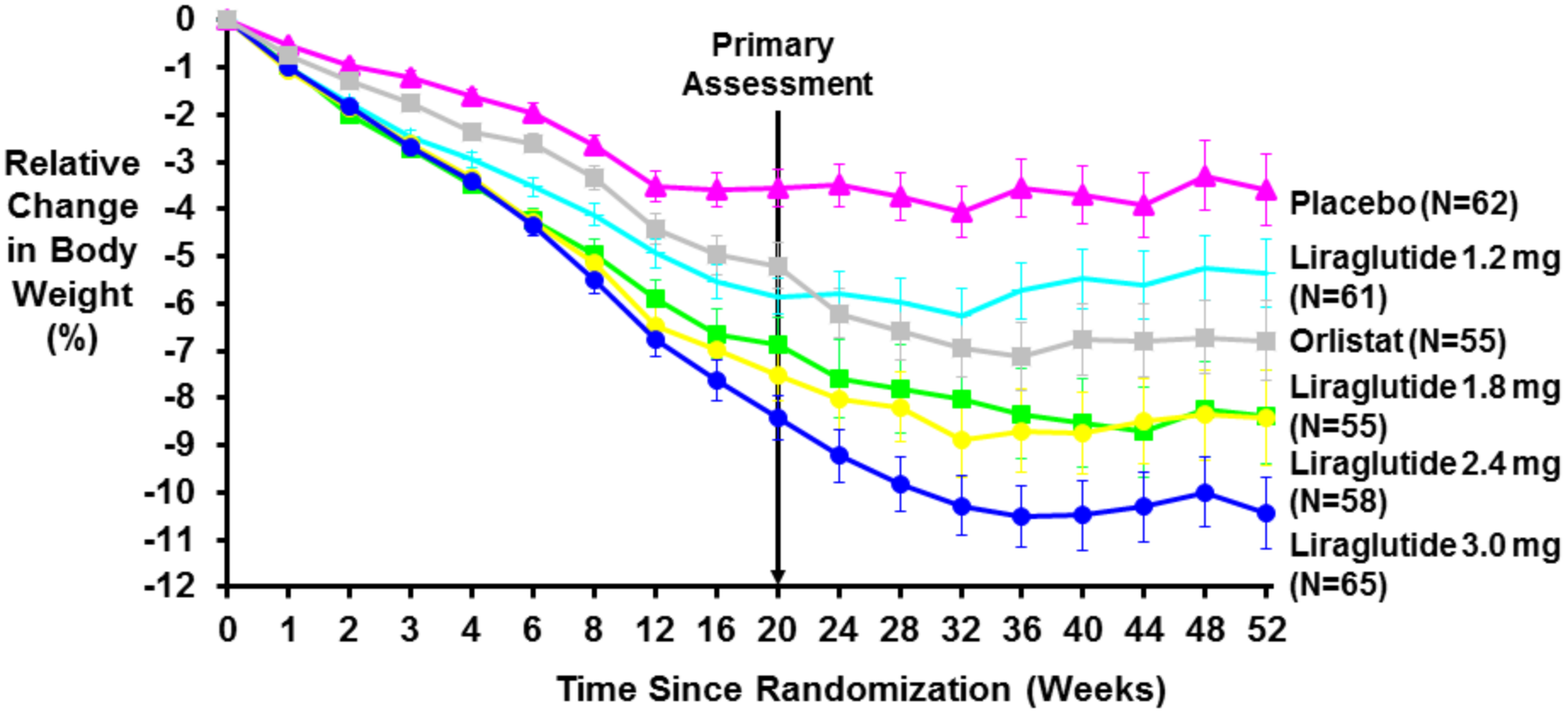


Weight Loss at Week 20 – Trial 1807



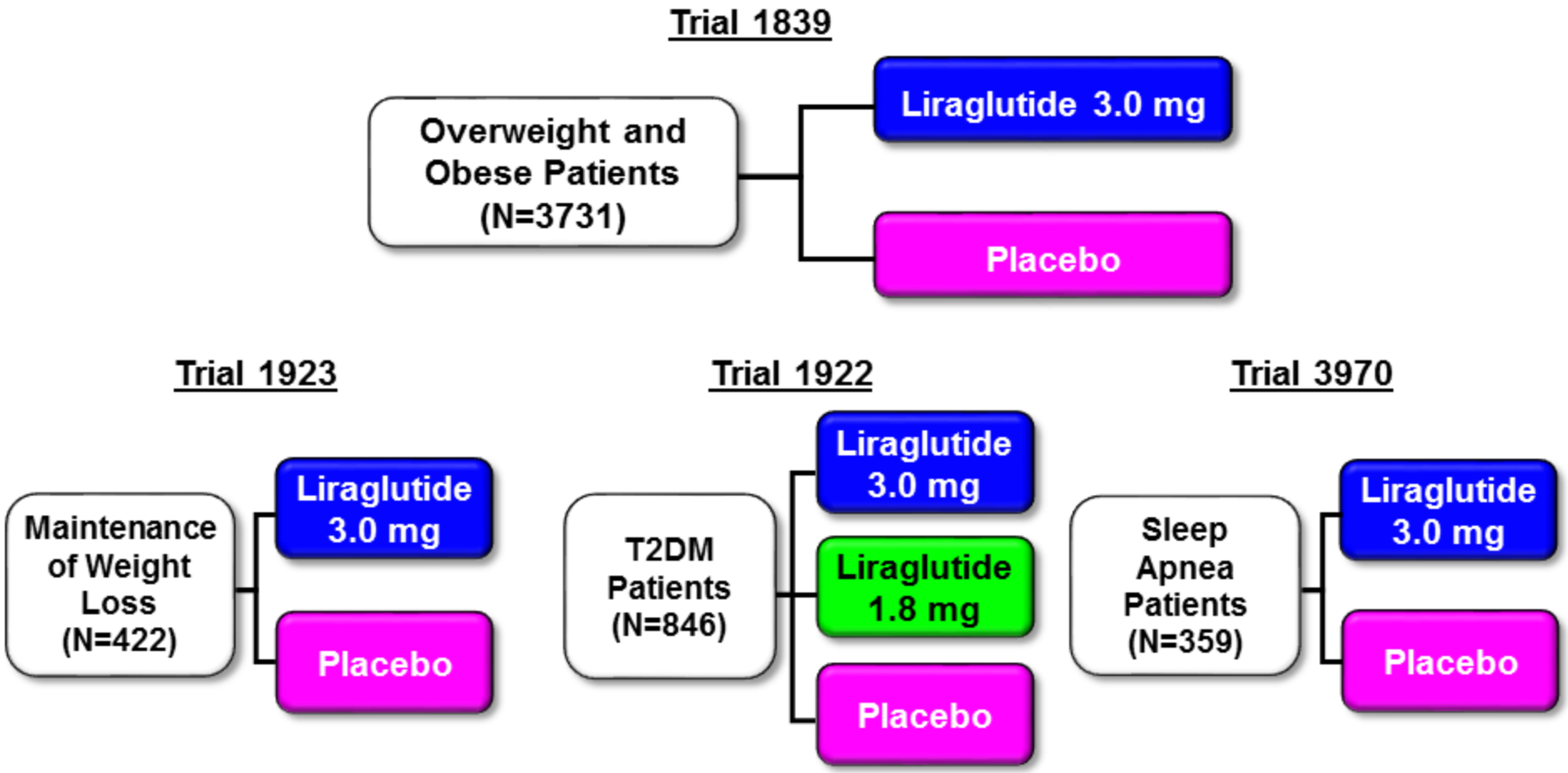
N = number of patients completing Week 20
Trial 1807; ITT; observed mean +/- SE

Optimal Weight Loss at Week 52 with Liraglutide 3.0 mg



N = number of patients completing Week 52
Trial 1807; ITT; observed mean +/- SE

Phase 3 Weight Management Clinical Development Program



T2DM: Type 2 Diabetes Mellitus
N: number of randomized patients

Consistent Design in Randomized, Placebo-Controlled Phase 3 Trials

- BMI ≥ 30 kg/m^2, or, ≥ 27 kg/m^2 with co-morbidity (dyslipidemia, hypertension, pre-diabetes/type 2 diabetes, obstructive sleep apnea)
- 4-week dose escalation period
- Stable body weight; previously failed diet intervention
- Individually counselled at each study visit
  - Reduce 500 kcal/day
  - Maintain/increase physical activity 150 min/wk

Same Statistical Analyses Used in Phase 3 Trials and Pooled Analyses

- Analysis of co-variance for continuous endpoints
- Logistic regression for dichotomous endpoints
- Last Observation Carried Forward (LOCF) for missing data
  - Supported by multiple sensitivity analyses
- Similar statistical methodology in pooled efficacy analyses

Demographics of Total and US Populations in Phase 3 Trials

	Total Trial Population (N = 5344)	US Trial Population (N =2718)
Age (mean, years) (SD)	47.0 (12.2)	47.6 (11.7)
Age (%)		
18-64 years	92.9	93.8
65-74 years	6.7	5.9
Sex (%), Women	70.8	72.3
Race (%)		
White	83.9	79.2
Black/African American	10.8	17.5
Ethnicity (%), Hispanic or Latino	10.3	11.4
BMI (mean, kg/m^2) (SD)	38.0 (6.5)	38.3 (6.7)
BMI (kg/m^2)		
27 – 29.9	5.5	6.0
30 – 34.9	32.2	30.0
35 – 39.9	30.4	30.0
≥ 40	31.8	34.0

Baseline Characteristics in Phase 3 Trials Representative of Target Population

	Obese (Trial 1839) (N = 3723)	Maintenance (Trial 1923) (N = 422)	T2DM (Trial 1922) (N = 844)	OSA (Trial 3970) (N = 355)
Comorbidities (%)				
Dyslipidemia	29.4	29.4	66.6	33.8
Hypertension	34.8	30.8	69.3	42.3
Both	16.9	15.4	49.9	21.4
Glycemic Status (%)				
Normoglycemia	38.8	35.5	0.0	35.5
Pre-diabetes*	61.2	64.5	0.0	64.5
Type 2 diabetes	0.0	0.0	100.0	0.0
History of CV Disease, %	8.6	9.7	14.9	5.9

N are the numbers of patients in the safety analysis set (patients receiving at least 1 dose of trial product)

* Pre-diabetes was defined by any of 3 criteria: impaired fasting glucose, impaired glucose tolerance, or HbA1c 5.7 to 6.4% (ADA 2010 criteria); SAS

Study Disposition in Phase 3 Trials: ~70% Patients Completed Trials

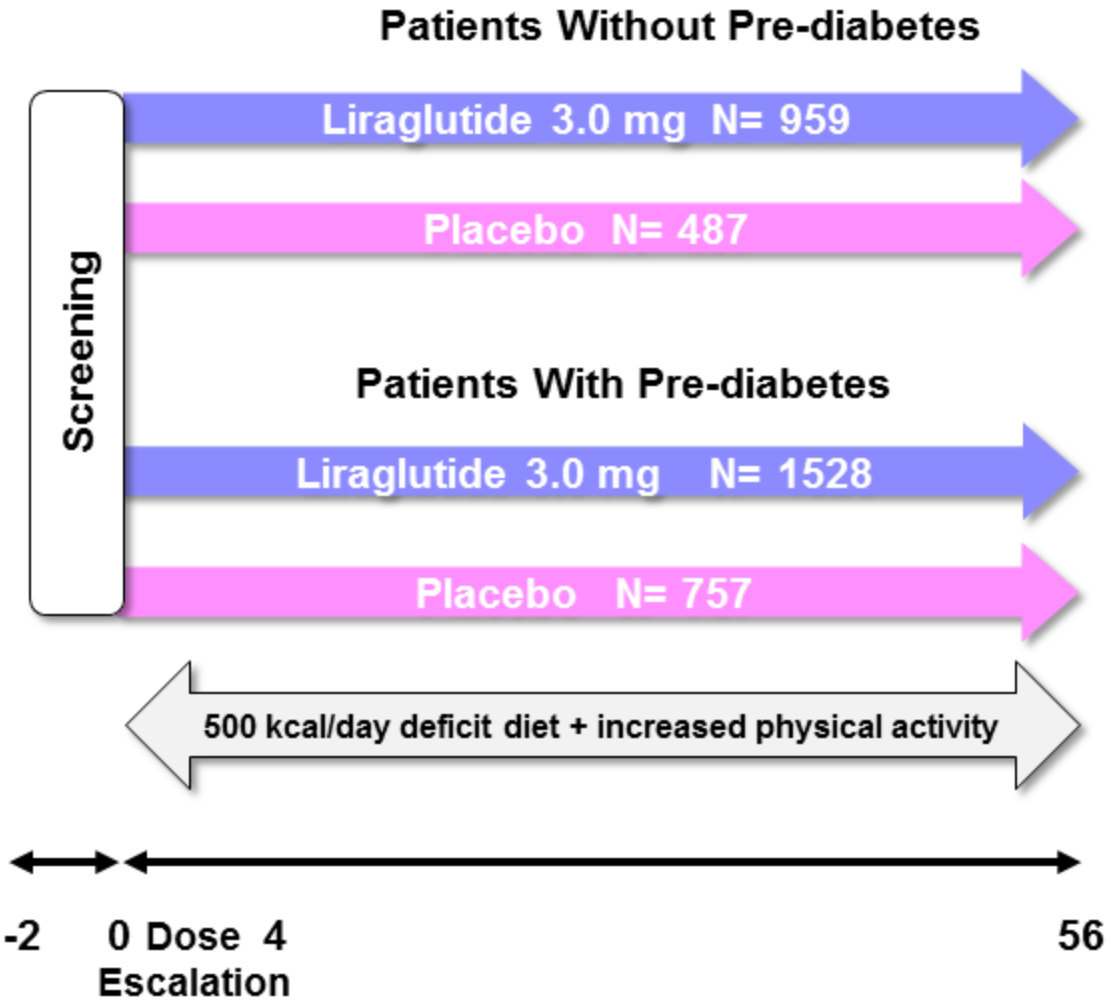
	Liraglutide 3.0 mg n (%)	Placebo n (%)
Randomized	3302	1845
Exposed	3291 (99.7)	1843 (99.9)
Completer	2406 (72.9)	1229 (66.6)
Withdrawn	896 (27.1)	616 (33.4)
Adverse event	327 (9.9)	79 (4.3)
Withdrawal consent	294 (8.9)	277 (15.0)
Non-compliance with protocol	93 (2.8)	61 (3.3)
Ineffective therapy	48 (1.5)	84 (4.6)
Other	134 (4.1)	115 (6.2)
Returning dropout*	238 (30.1)	250 (30.0)

*Trials 1839, 1922, and 1923
n: number of patients
Other includes pregnancy, use of insulin, GLP1RA or DPP-IV, unacceptable hyperglycemia, diagnosis of T1DM/T2DM

Trial 1839 Design: Weight Loss in Obese or Overweight Patients without Diabetes

3731 overweight/obese patients

Randomization 2:1 - liraglutide 3.0 mg: placebo

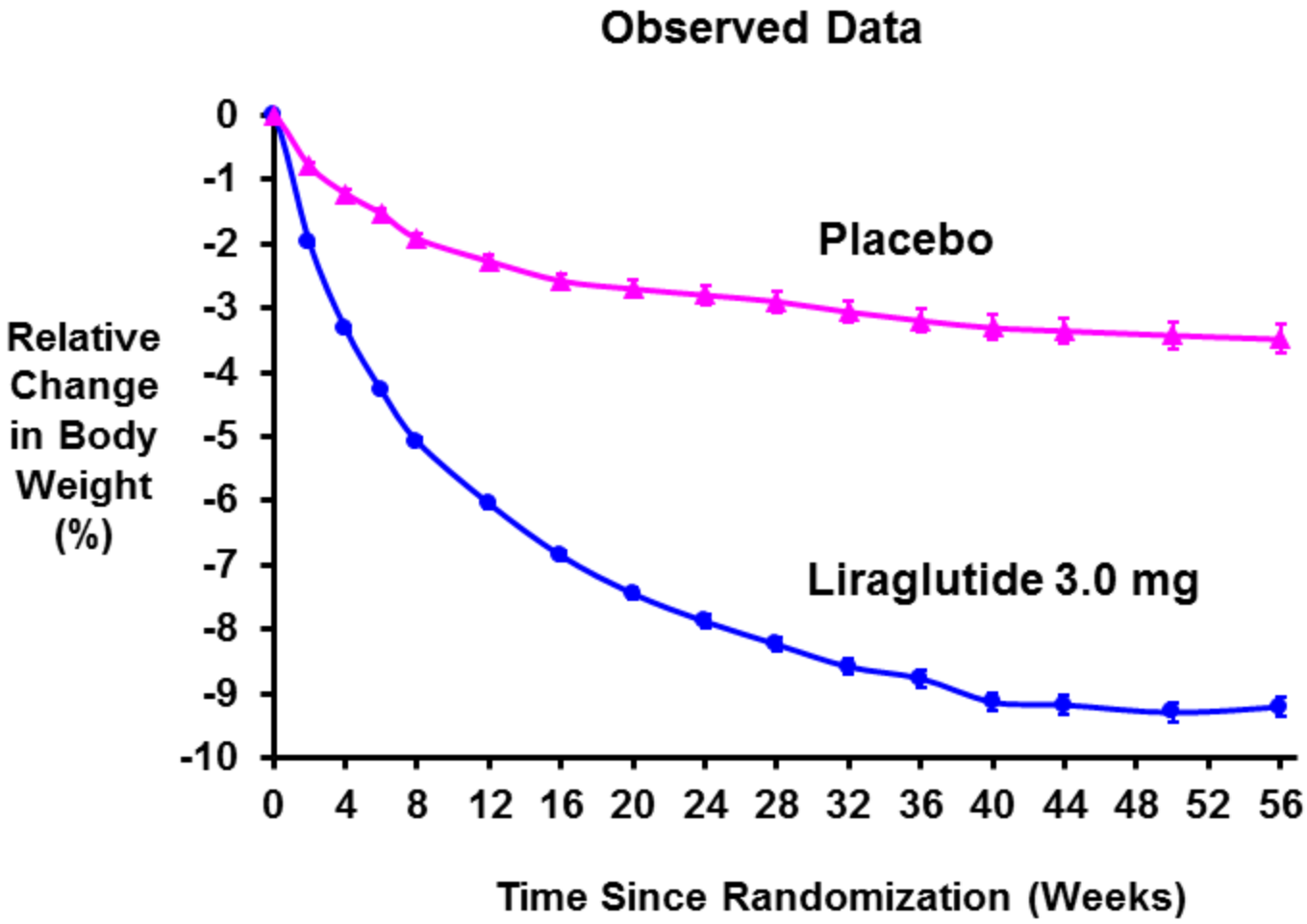


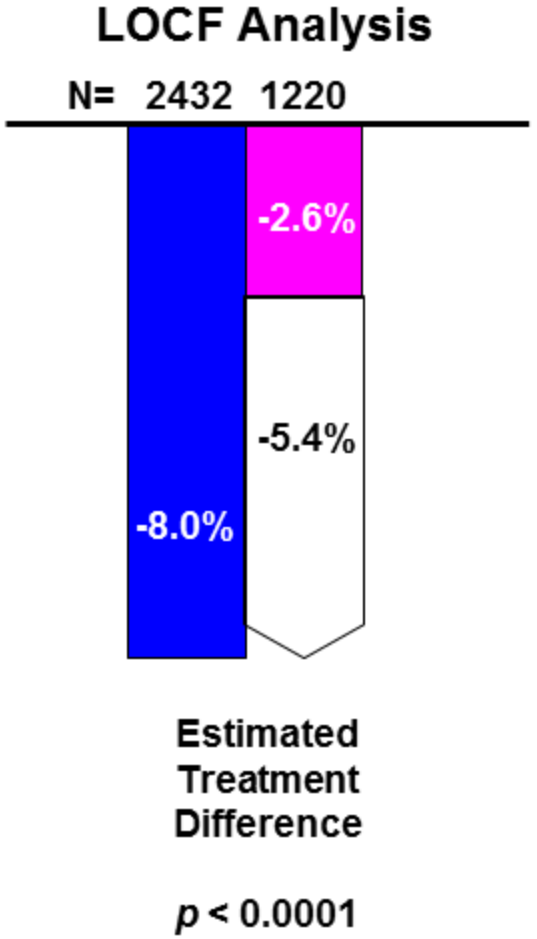
Pre-diabetes was defined by any of 3 criteria: impaired fasting glucose, impaired glucose tolerance, or HbA1c 5.7 to 6.4% (ADA 2010 criteria)

Trial 1839: Co-Primary Endpoints

- Change in % body weight from baseline
- % patients ≥ 5% reduction baseline body weight
- % patients > 10% reduction baseline body weight

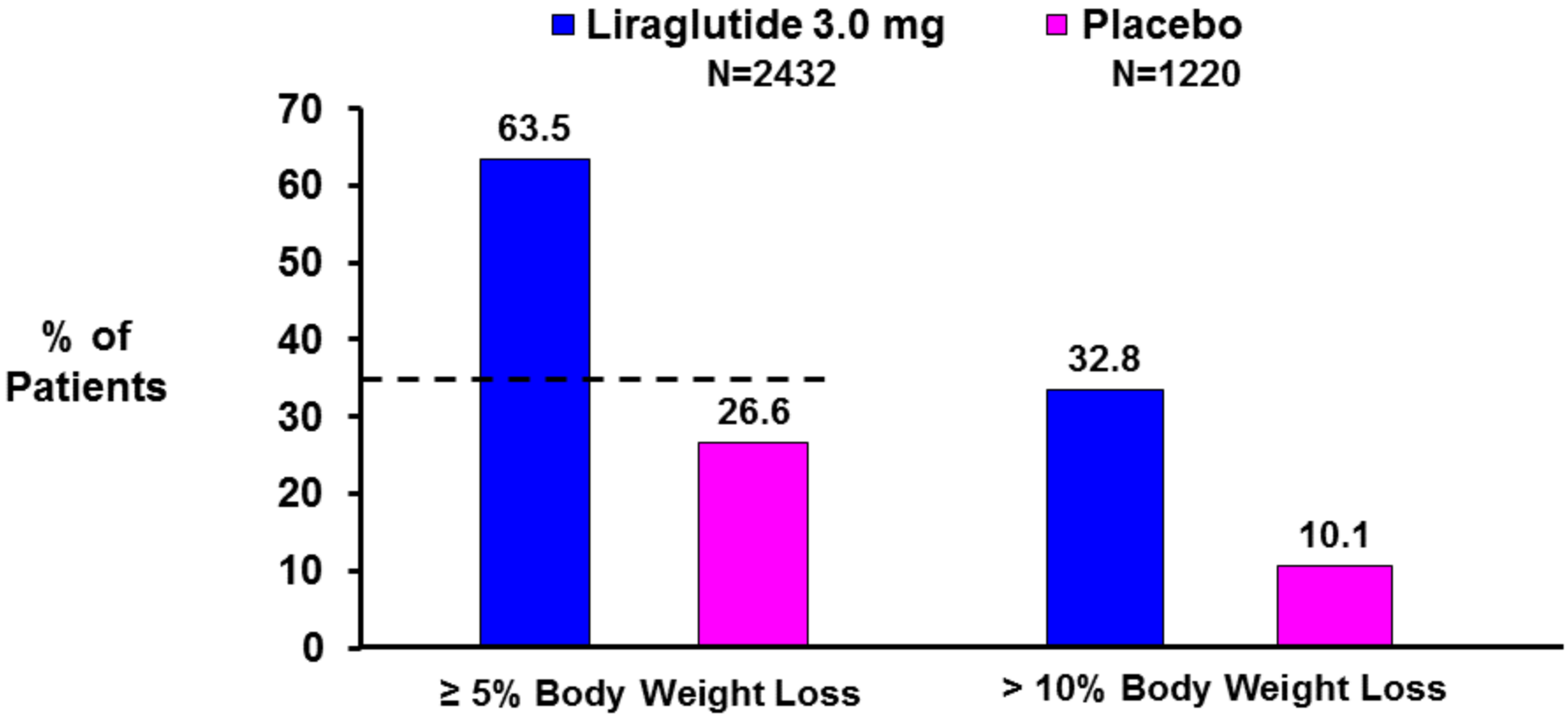
Trial 1839: Patients Lost Significantly More Weight with Liraglutide 3.0 mg





Observed mean +/- SE for patients completing each scheduled visit
FAS with LOCF; N: number of patients contributing to analysis; Data are LSMeans.

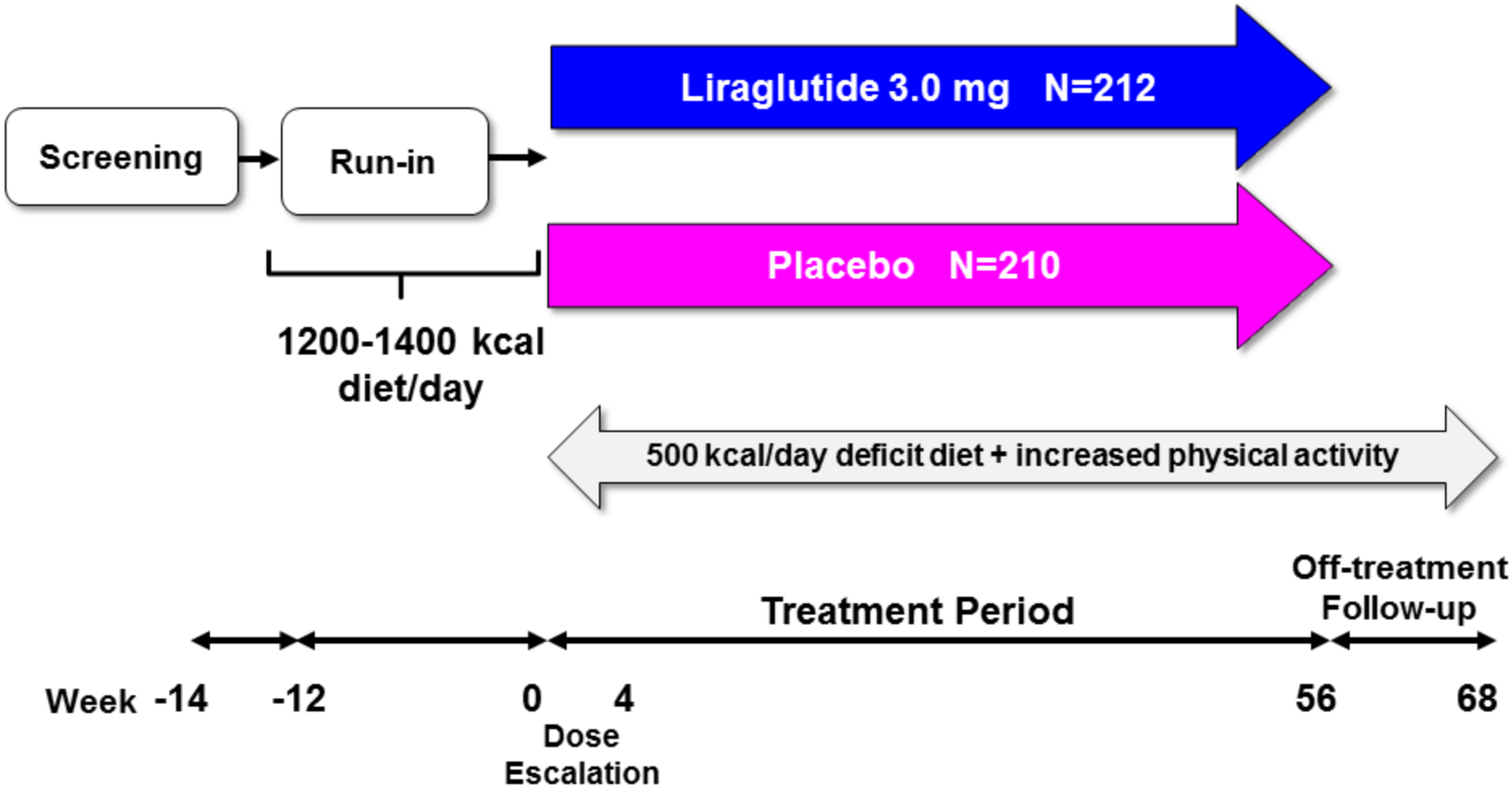
Trial 1839: Significantly More Patients Lost ≥ 5% or > 10% Weight with Liraglutide 3.0 mg



Odds Ratio (95% CI):	4.8 (4.1, 5.6)	4.3 (3.5, 5.3)
p-value:	< 0.0001	< 0.0001

FAS with LOCF; N: number of patients contributing to analysis; data are LSMeans.

Trial 1923 Design: Maintenance After Weight Loss with Low Calorie Diet

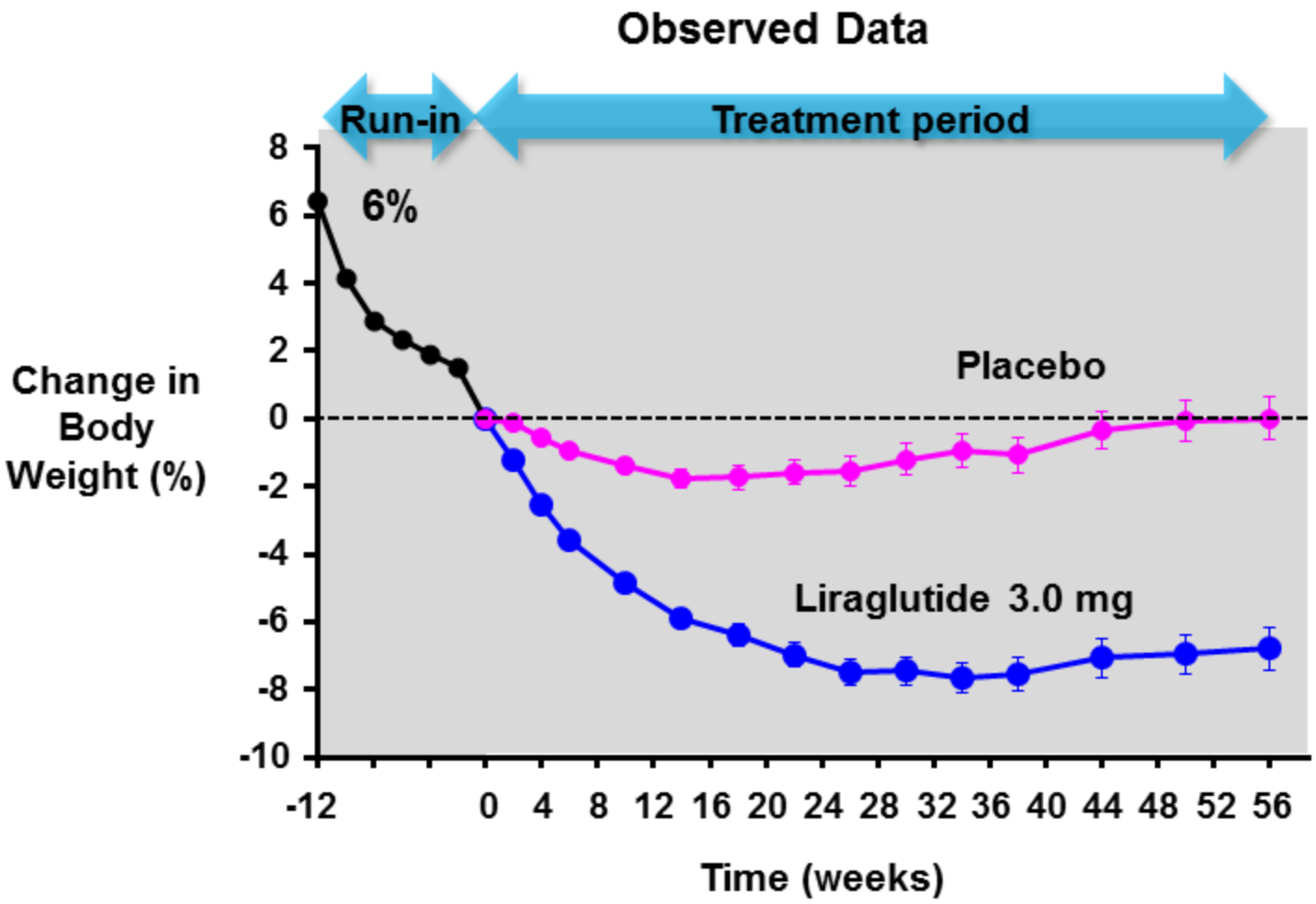


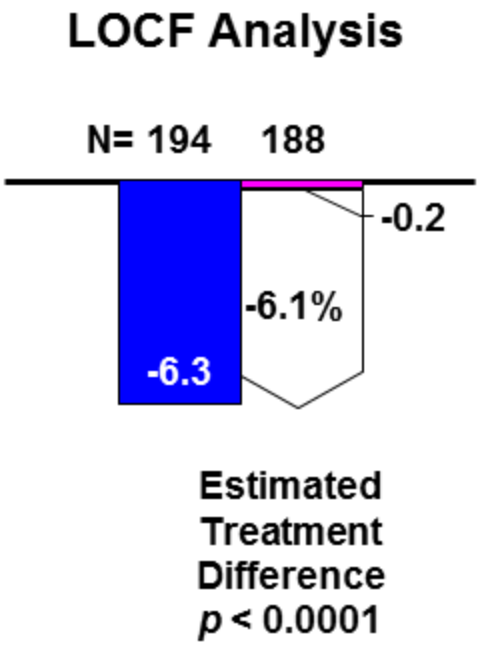
422 overweight/obese patients, Randomization 1:1 liraglutide 3.0 mg:placebo

Trial 1923: Co-Primary Endpoints for Weight Maintenance

- Change in body weight from baseline (randomization)
- % people maintaining body weight achieved during low calorie diet run-in period
- % people achieving additional ≥ 5% weight loss from baseline (randomization)

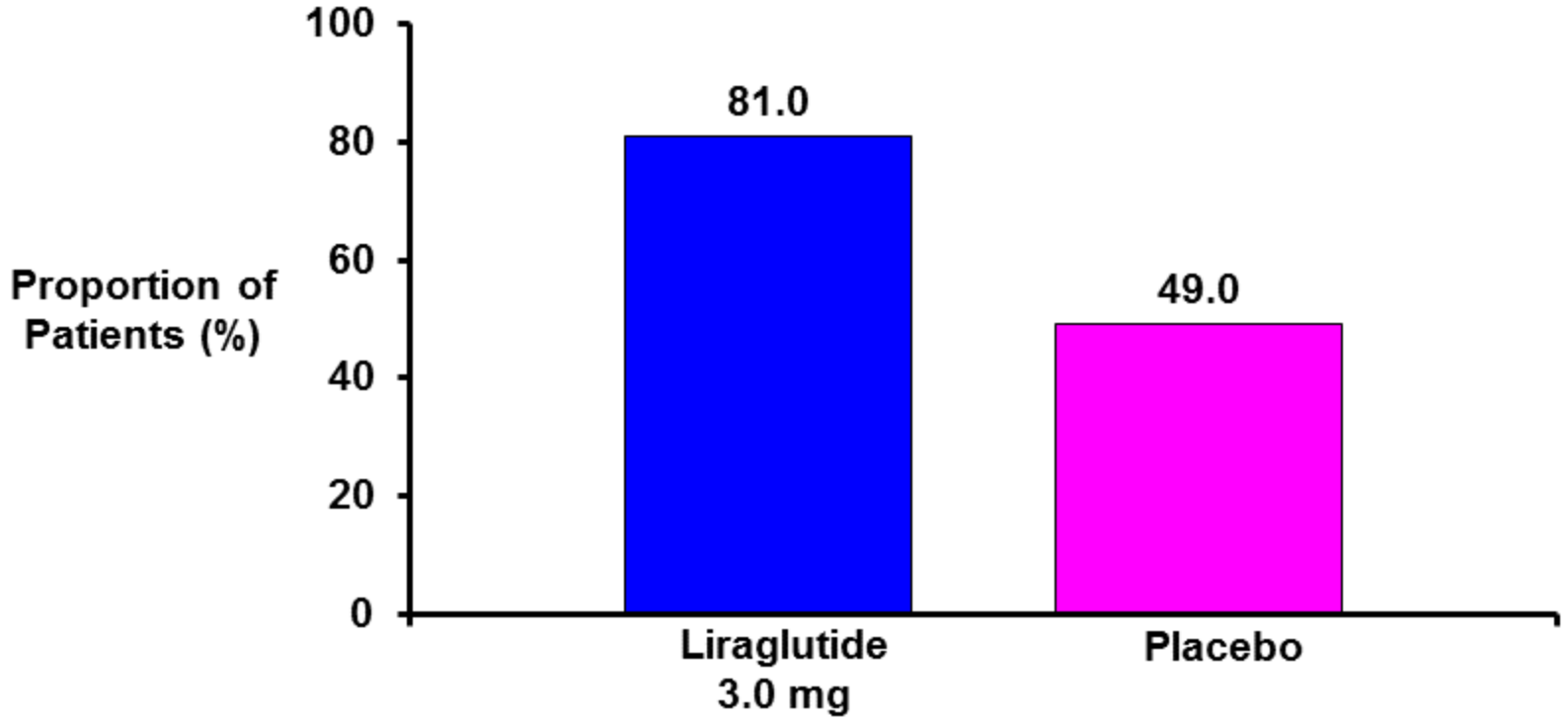
Trial 1923: Significant Further Weight Loss with Liraglutide 3.0 mg After LCD Run-in





LCD = low calorie diet
Observed mean +/- SE for patients completing each scheduled visit
FAS with LOCF; N: number of patients contributing to analysis; data are LSMeans.

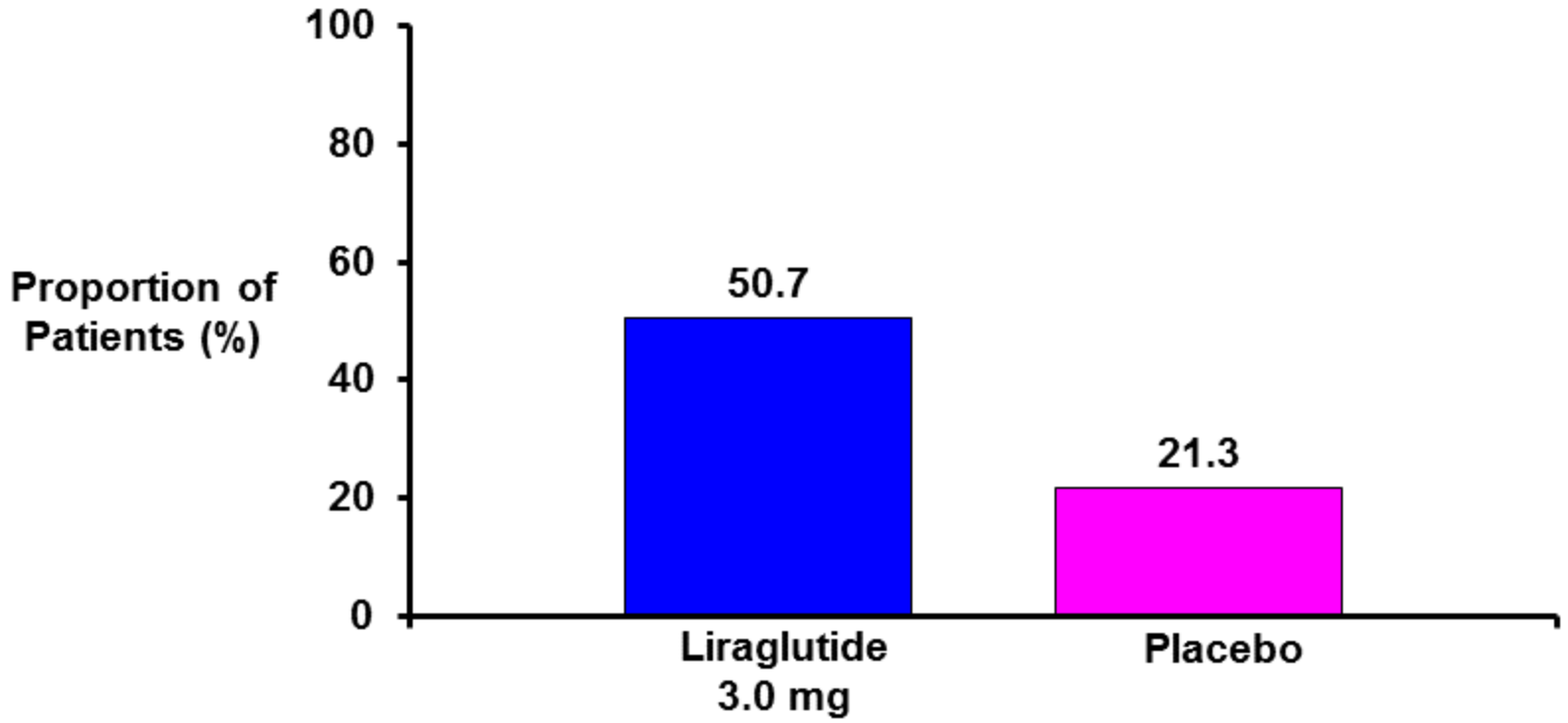
Trial 1923: More Patients Maintained Weight Loss with Liraglutide 3.0 mg



N	194	188
Odds Ratio (95% CI):	4.8 (3.0, 7.7)	
p-value:	< 0.0001	

FAS with LOCF; N: number of patients contributing to analysis; data are LSMeans.
"Maintenance" defined as regain of no more than 0.5% of baseline weight.

Trial 1923: More Patients Lost ≥ 5% Additional Weight with Liraglutide 3.0 mg



N	194	188
Odds Ratio (95% CI):	3.8 (2.4, 6.0)	
p-value:	< 0.0001	

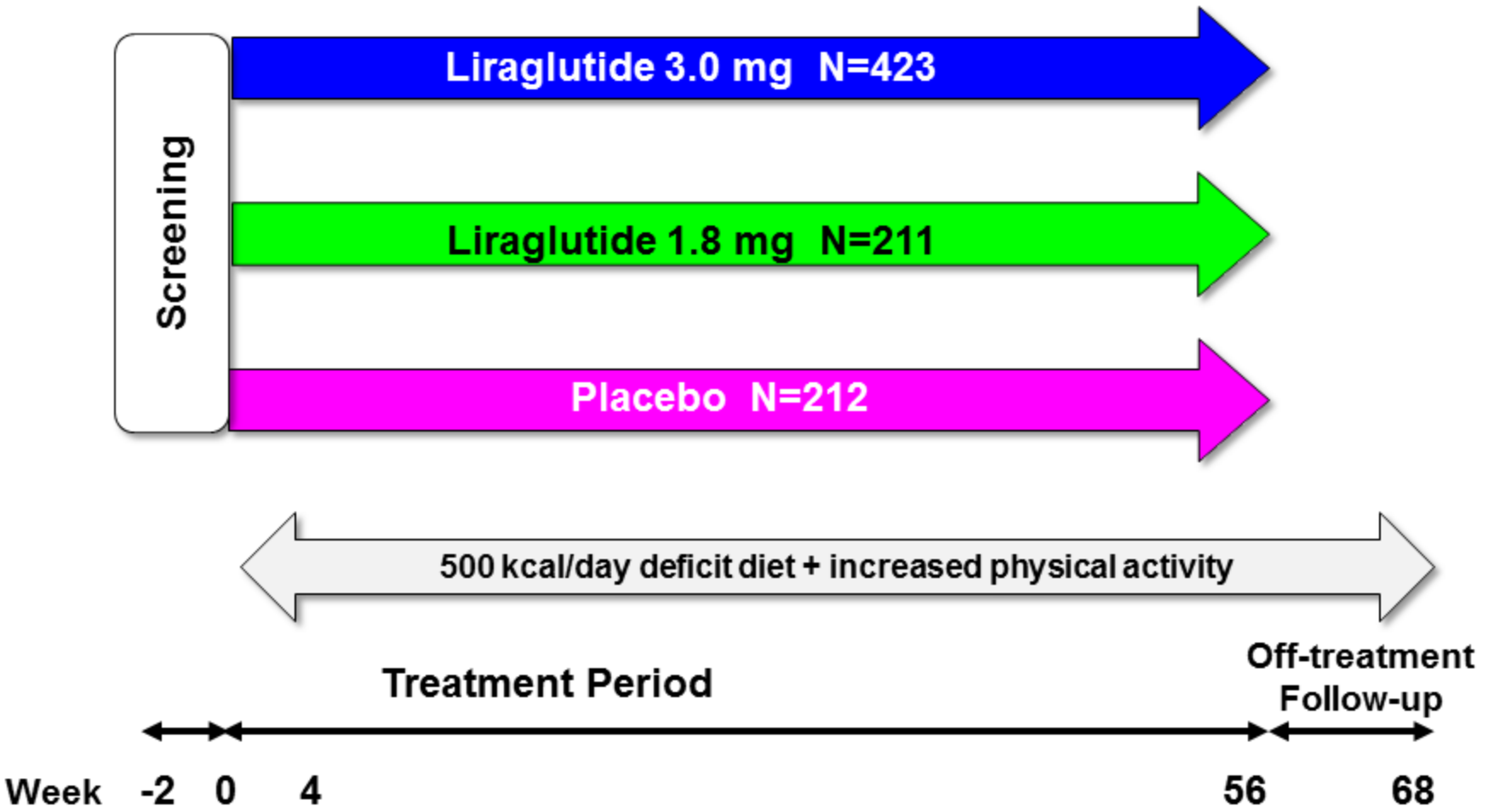
FAS with LOCF; N: number of patients contributing to analysis; data are LSMeans.

Trial 1922: Type 2 Diabetes Patients

- Obesity increases lifetime risk of diabetes to ~50% in adults 45 years old[1]
- 80-90% of patients with T2DM are overweight or obese[2]
- Difficult for people with diabetes to lose weight[3]

1. Narayan et al (2007) Diabetes Care 30:1562–1566
2. Wing RR. Weight loss in the management of type 2 diabetes. Gerstein HC, Haynes RB, editors. Evidence-based Diabetes Care. 252-276. 2000. B.C. Decker, Inc
3. Pi Sunyer Diabetes Care June 2005 vol. 28 no. 6 1526-1527

Trial 1922 Design: Weight Loss in Patients with Type 2 Diabetes



Trial 1922: Baseline Characteristics of Patients with Type 2 Diabetes

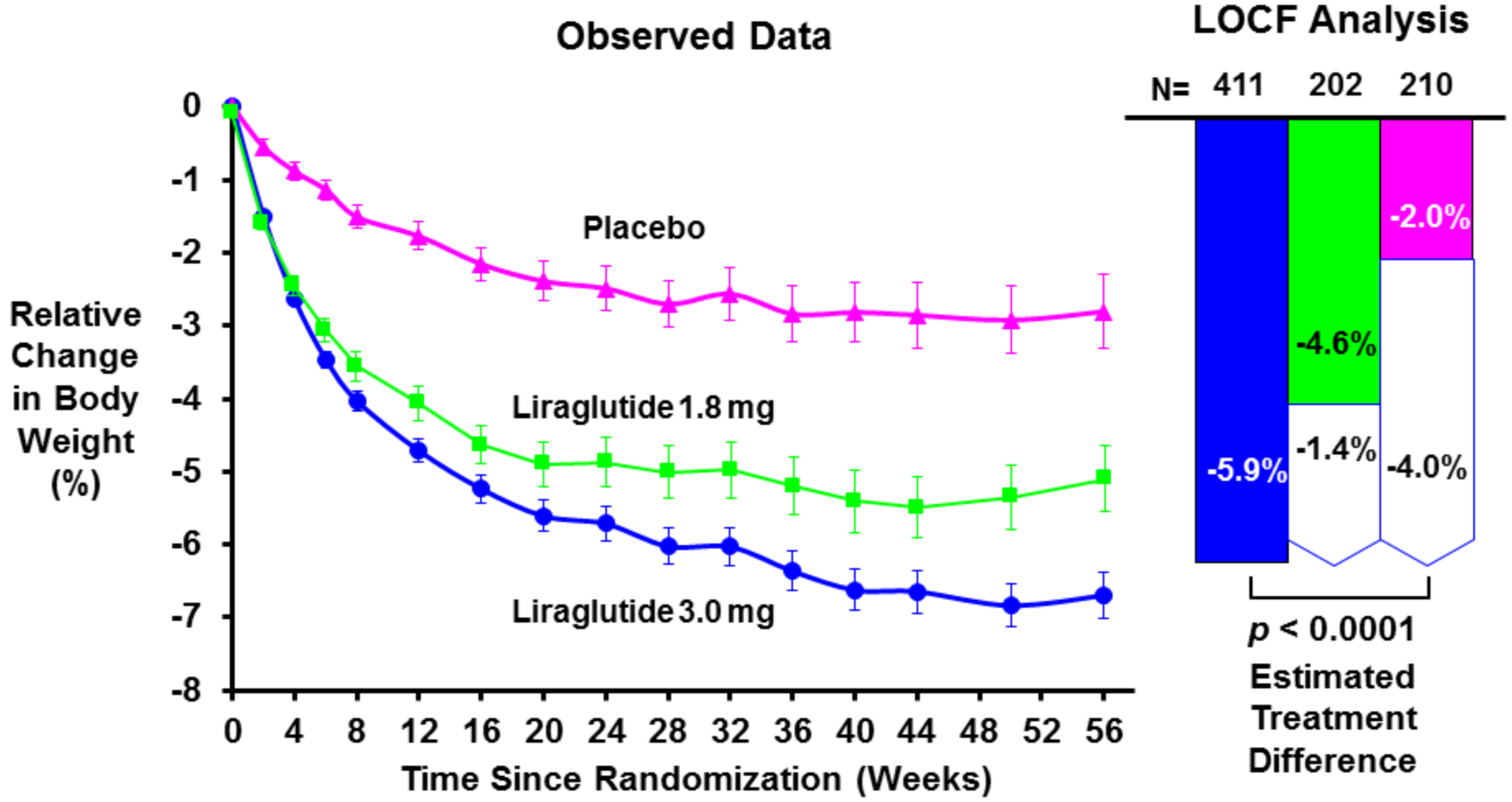
	Liraglutide 3.0 mg (N = 423)	Liraglutide 1.8 mg (N = 211)	Placebo (N = 212)
Age (Mean, SD)	55.0 (10.8)	54.9 (10.7)	54.7 (9.8)
Sex, Male (%)	52.0	51.2	45.8
BMI (Mean, SD)	37.1 (6.5)	37.0 (6.9)	37.4 (7.1)
Diabetes Duration (yrs) (Mean, SD)	7.5 (5.7)	7.4 (5.2)	6.7 (5.1)
Background Diabetes Treatment (%)			
Diet and Exercise	11.2	14.2	9.5
Metformin Monotherapy	57.5	54.4	59.7
Metformin + Glitazone	5.3	6.4	4.7
SU Monotherapy/combo	26.0	25.0	26.1
HbA1c (%) (Mean, SD)	7.9 (0.8)	8.0 (0.8)	7.9 (0.8)
Comorbidities (%)			
Hypertension	69.3	70.1	68.4
Dyslipidemia	69.7	67.8	59.4
Hypertension and Dyslipidemia	52.0	52.1	43.4
History of CV Disease (%)	16.4	14.8	12.3

SD = standard deviation; based on randomized patients (except background diabetes treatment – based on FAS)

Trial 1922: Co-Primary Endpoints

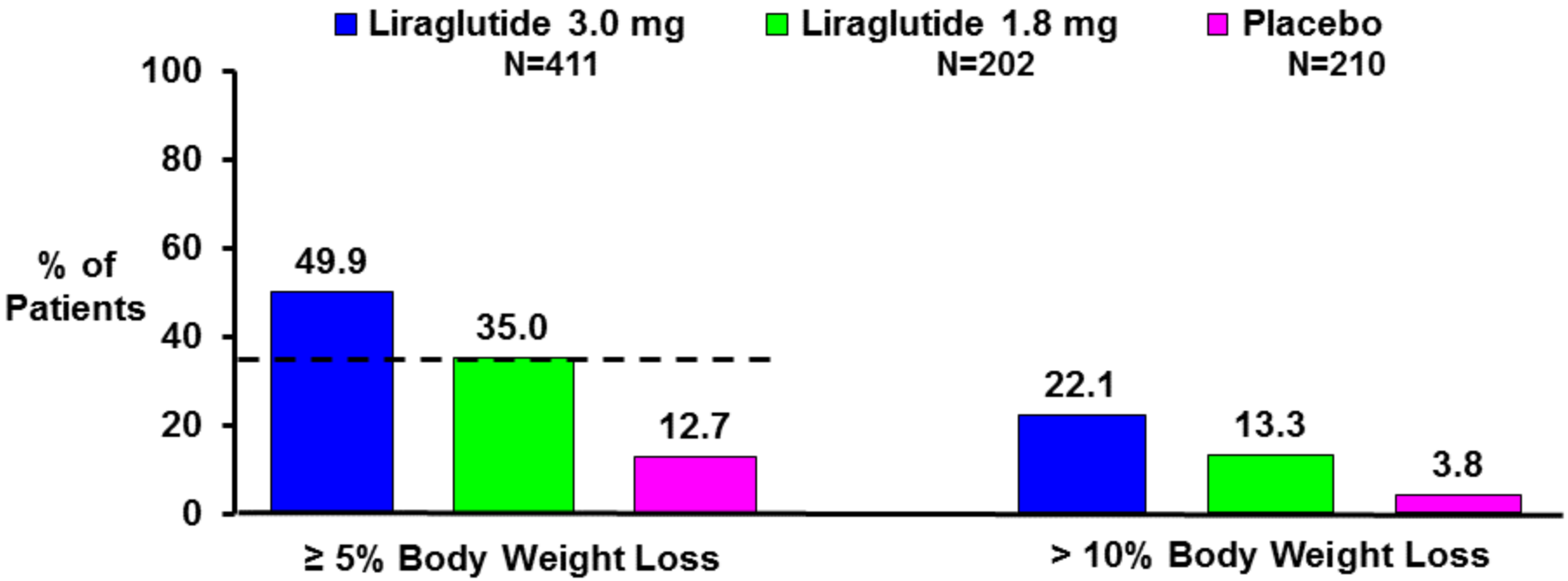
- Change in body weight from baseline
- % patients ≥ 5% reduction baseline body weight
- % patients > 10% reduction baseline body weight

Trial 1922: Patients with T2DM Lost Significantly More Weight on Liraglutide 3.0 mg



Observed mean +/- SE for patients completing each scheduled visit
FAS with LOCF; N: number of patients contributing to analysis; data are LSMeans.

Trial 1922: Significantly More Patients with T2DM Lost ≥ 5% or > 10% Weight with Liraglutide 3.0 mg



Odds Ratio vs. Placebo	6.8	3.7
95% CI	4.3, 10.7	2.2, 6.1
p-value	< 0.0001	< 0.0001

Odds Ratio vs. Placebo	7.1	3.8
95% CI	3.5, 14.5	1.8, 8.4
p-value	< 0.0001	< 0.001

FAS with LOCF; N: number of patients contributing to analysis; data are LSMeans.

Trial 3970: Sleep Apnea, a Common Weight-Related Co-Morbidity

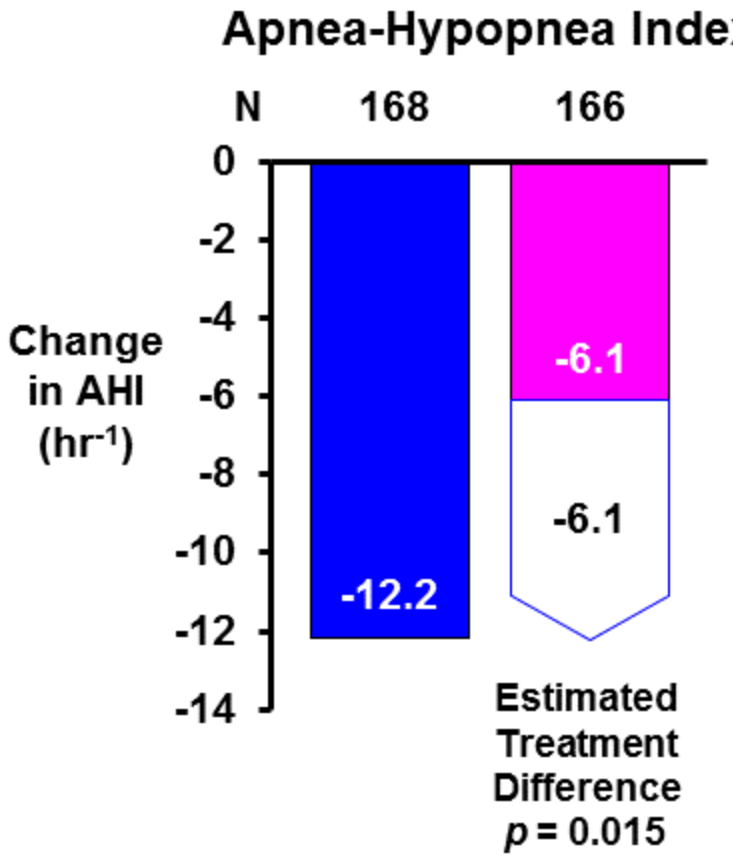
- Linked to obesity[1,2,3]
- Increases risk of hypertension, cardiovascular disease, other comorbidities[2,3]
- Weight loss is a cornerstone treatment[2,3]

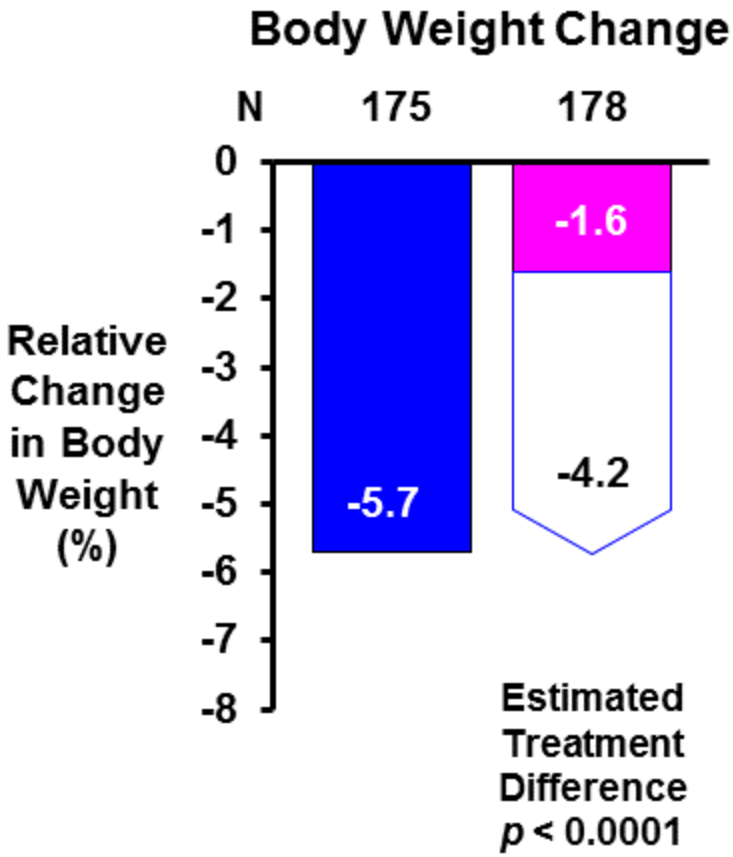
1. Strobel and Rosen (1996) Sleep 19(2): 104-115
2. Ronero-Corral et al (2010) Chest 137 (3): 711-719
3. Tuomilehto et al (2013) Sleep Med Rev 17(5): 321-329

Trial 3970: Change in Apnea-Hypopnea Index (AHI) and Body Weight at 32 Weeks

Baseline AHI: 49 hr^{-1}

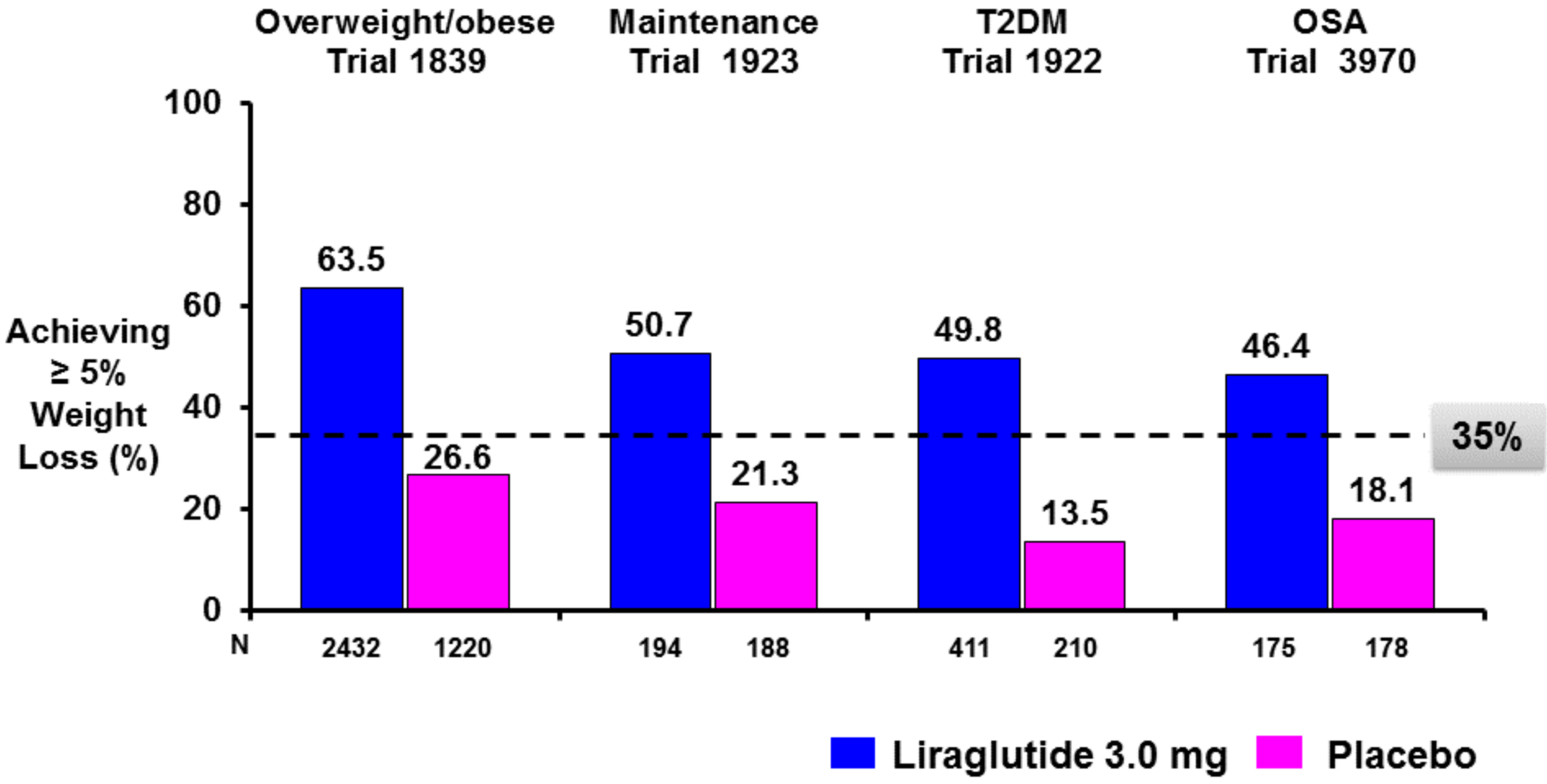
■ Liraglutide 3.0 mg ■ Placebo





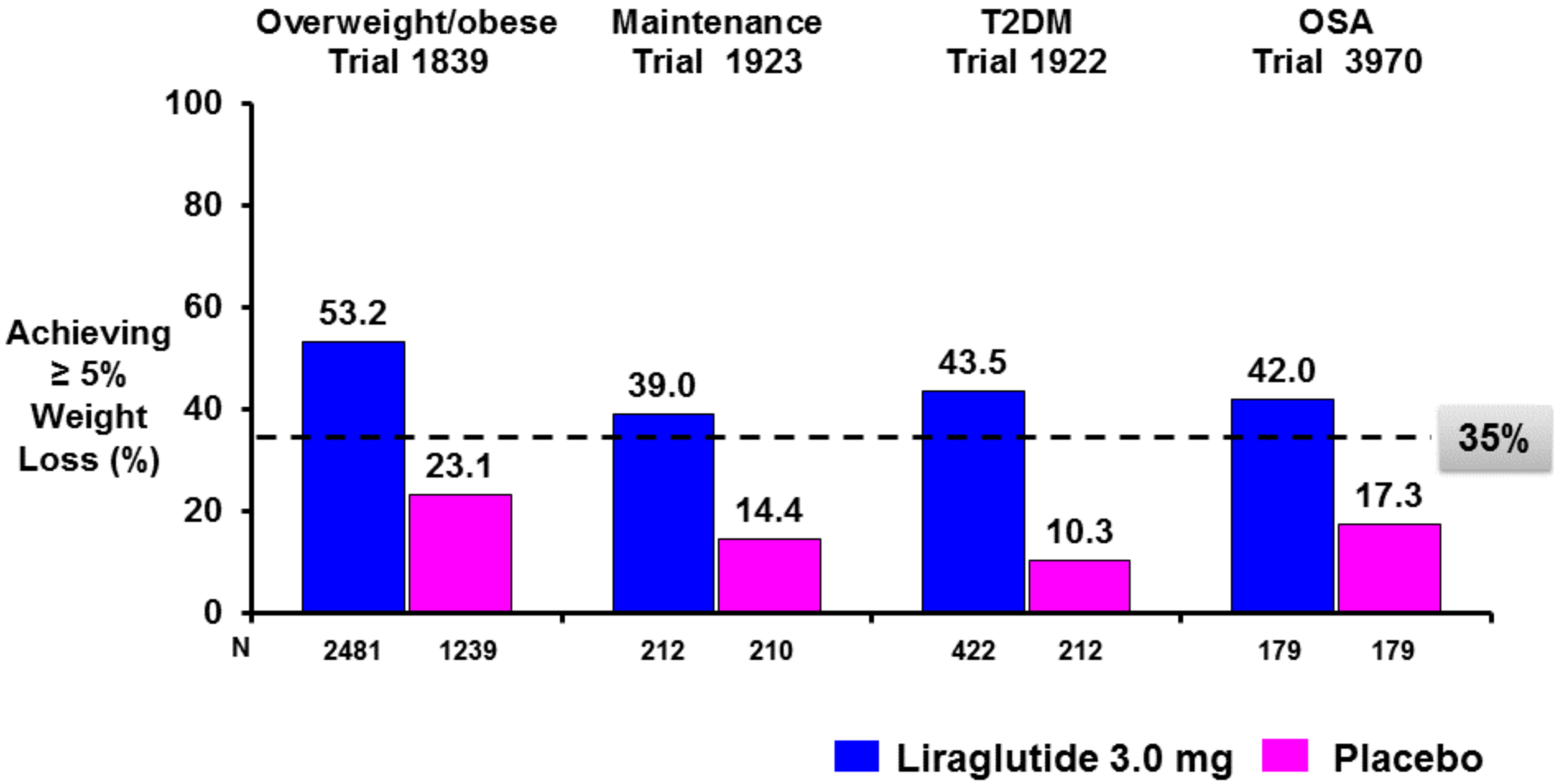
FAS with LOCF; N: number of patients contributing to analysis; data are LSMeans.

Patients Achieved Clinically Meaningful Weight Loss with Liraglutide 3.0 mg Across All Trials



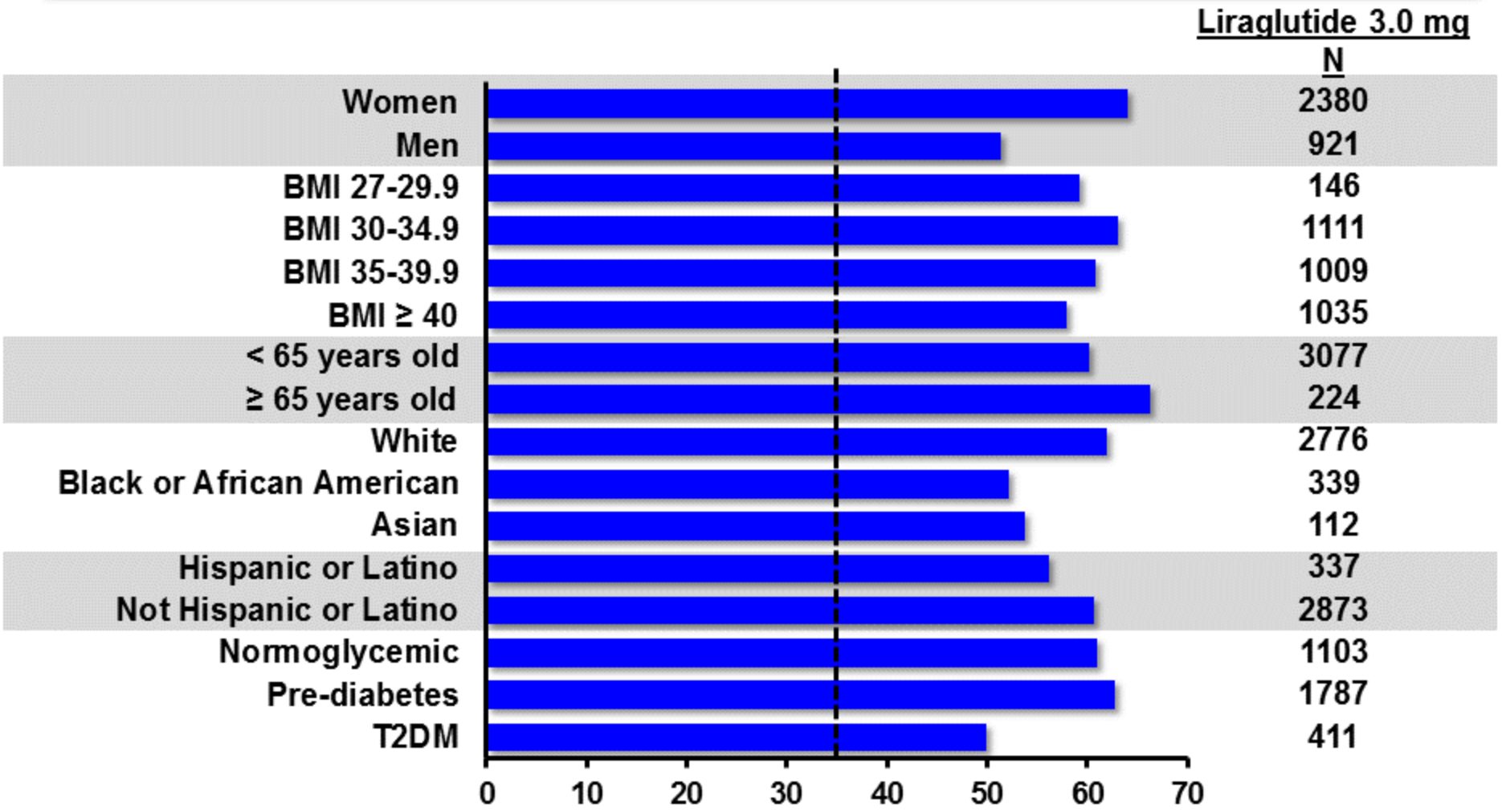
FAS; Estimates from a logistic regression analysis for the FAS with LOCF; LSMeans. N, number of patients contributing to analysis; responder rate ratios >2 across all trials.

Sensitivity Analysis Also Met FDA Benchmark: Withdrawals Counted as Non-Responders



All randomized; LSMeans. N, number of patients contributing to analysis; responder rate ratios >2 across all trials.

Liraglutide 3.0 mg Met FDA Categorical Benchmark in All Subgroups Studied

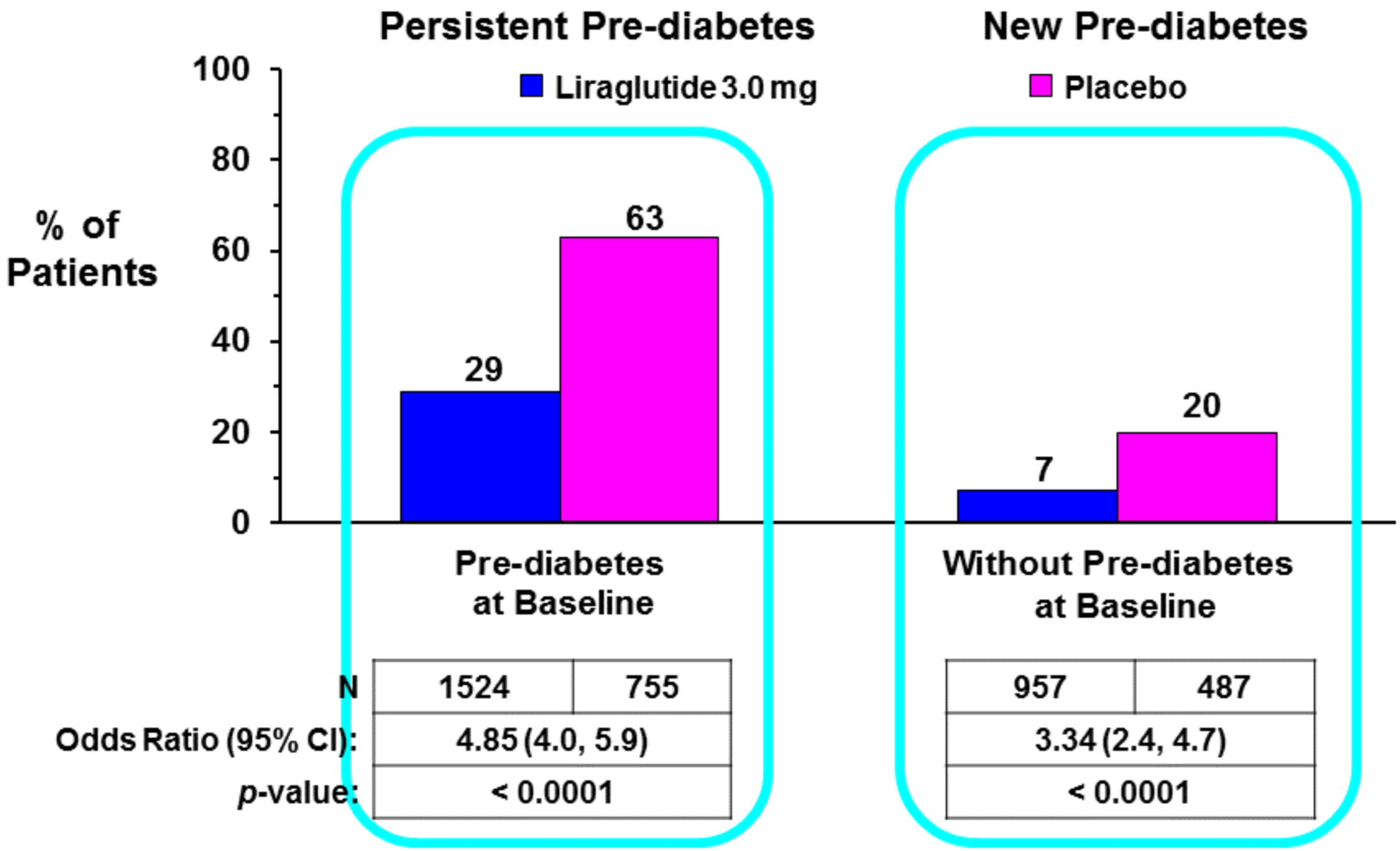


Pooled Phase 2 and 3 trials
FAS with LOCF

Secondary Endpoints Address Complexities and Complications of Obesity

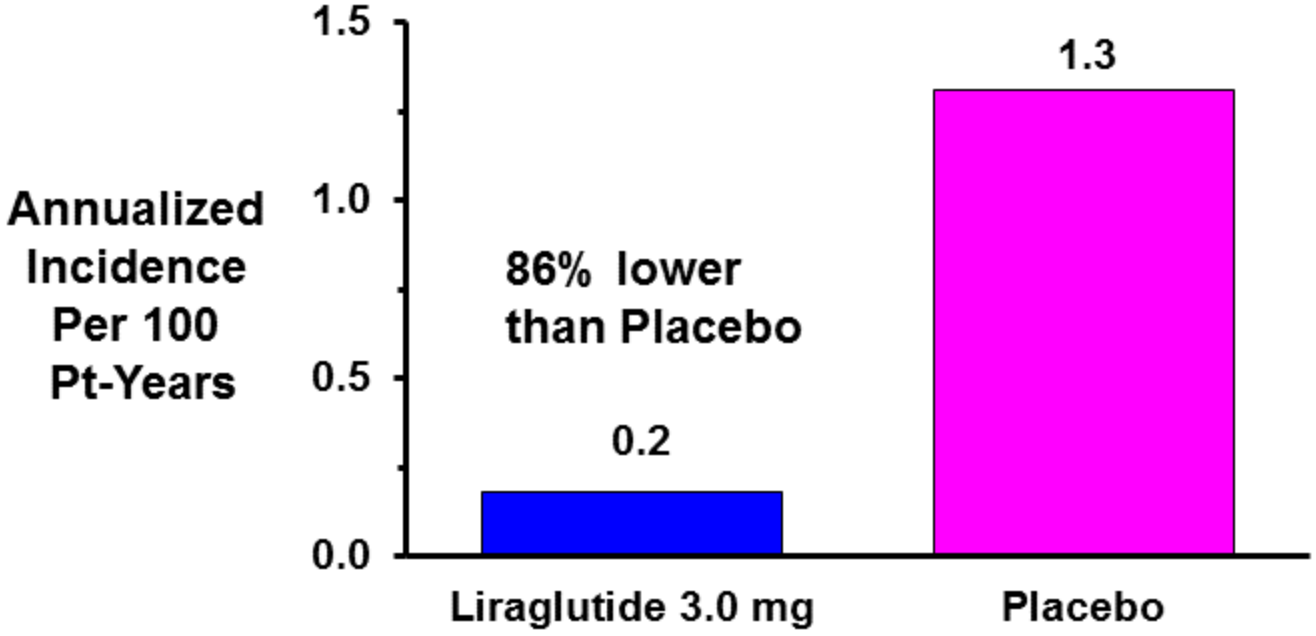
- Pre-diabetes/progression to T2DM diagnosis
- Glycemic parameters in patients with T2DM
- Cardiometabolic parameters
  - Waist circumference
  - Blood pressure
  - Lipids
  - Cardiovascular risk markers
- Quality of life

Trial 1839: Diagnosis of Pre-Diabetes Decreased with Liraglutide 3.0 mg



FAS with LOCF; N: number of patients contributing to analysis; data are LSMeans.

Trial 1839: Liraglutide Reduced Incidence of Type 2 Diabetes



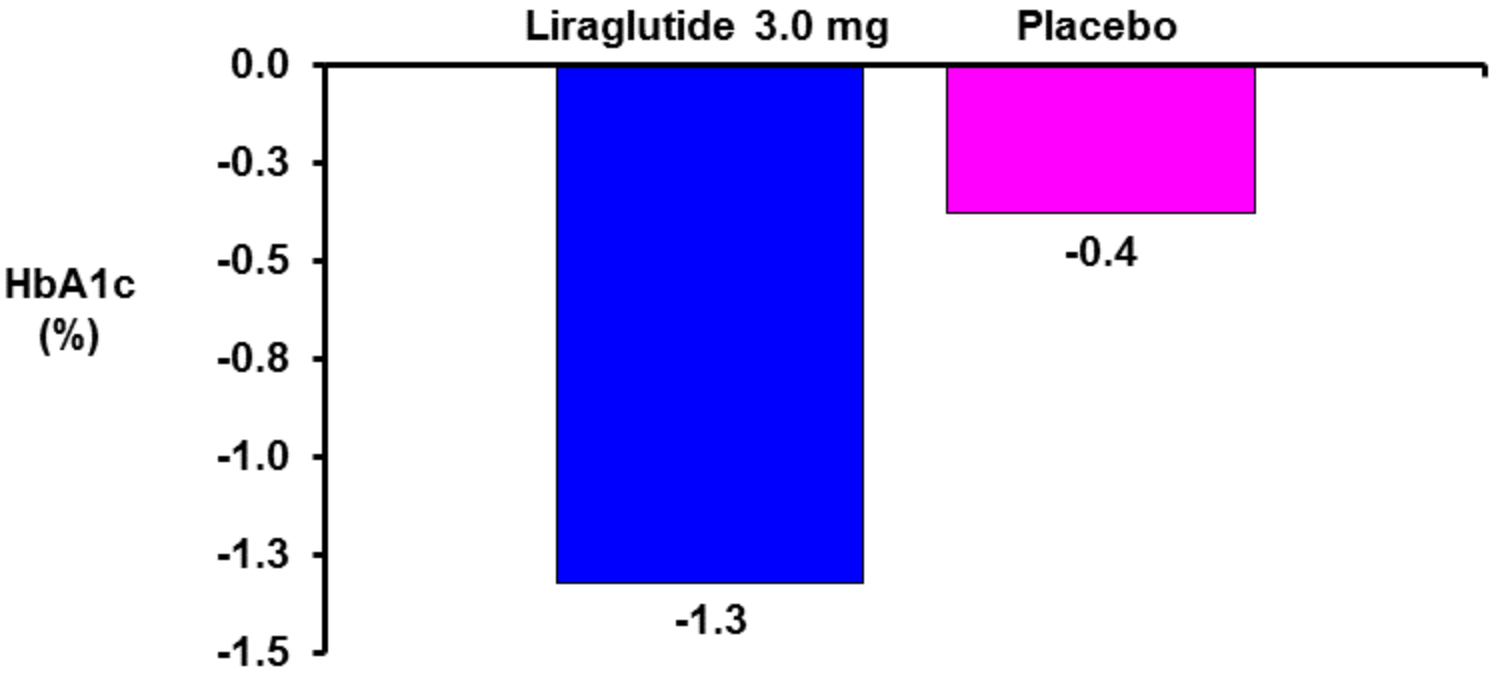
N	2437	1225
Odds Ratio (95% CI):	0.12 (0.04, 0.39)	
p-value:	< 0.001	

FAS with LOCF; N: number of patients contributing to analysis; data are LSMeans.
Diagnosis of type 2 diabetes based on HbA1c ≥ 6.5% or FPG ≥ 126 mg/dL or 2-hr post-challenge OGTT plasma glucose ≥ 200 mg/dL (at two consecutive visits)

Secondary Endpoints Address Complexities and Complications of Obesity

- Pre-diabetes/progression to T2DM diagnosis
- Glycemic parameters in patients with T2DM
- Cardiometabolic parameters
  - Waist circumference
  - Blood pressure
  - Lipids
  - Cardiovascular risk markers
- Quality of life

Trial 1922: Liraglutide Significantly Reduced HbA1c in T2DM



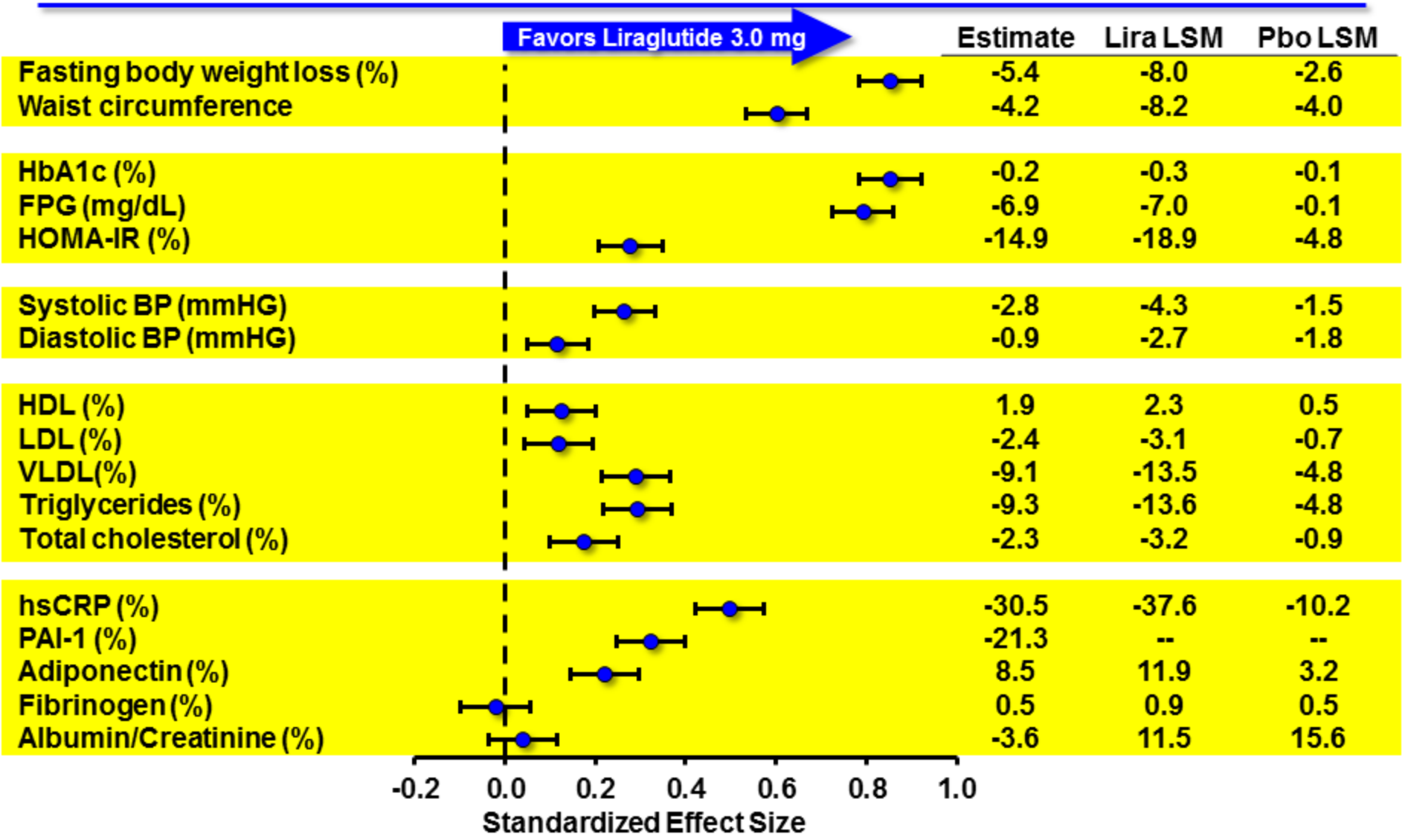
N	402	206
Baseline HbA1c (%)	7.9	7.9
End of Trial/LOCF	6.6	7.6
Treatment Difference	-0.9	
p-value	< 0.0001	

FAS with LOCF; N: number of patients contributing to analysis. Data are LSMeans. End of trial data are observed means.

Secondary Endpoints Address Complexities and Complications of Obesity

- Pre-diabetes/progression to T2DM diagnosis
- Glycemic parameters in patients with T2DM
- Cardiometabolic parameters
  - Waist circumference
  - Blood pressure
  - Lipids
  - Cardiovascular risk markers
- Quality of life

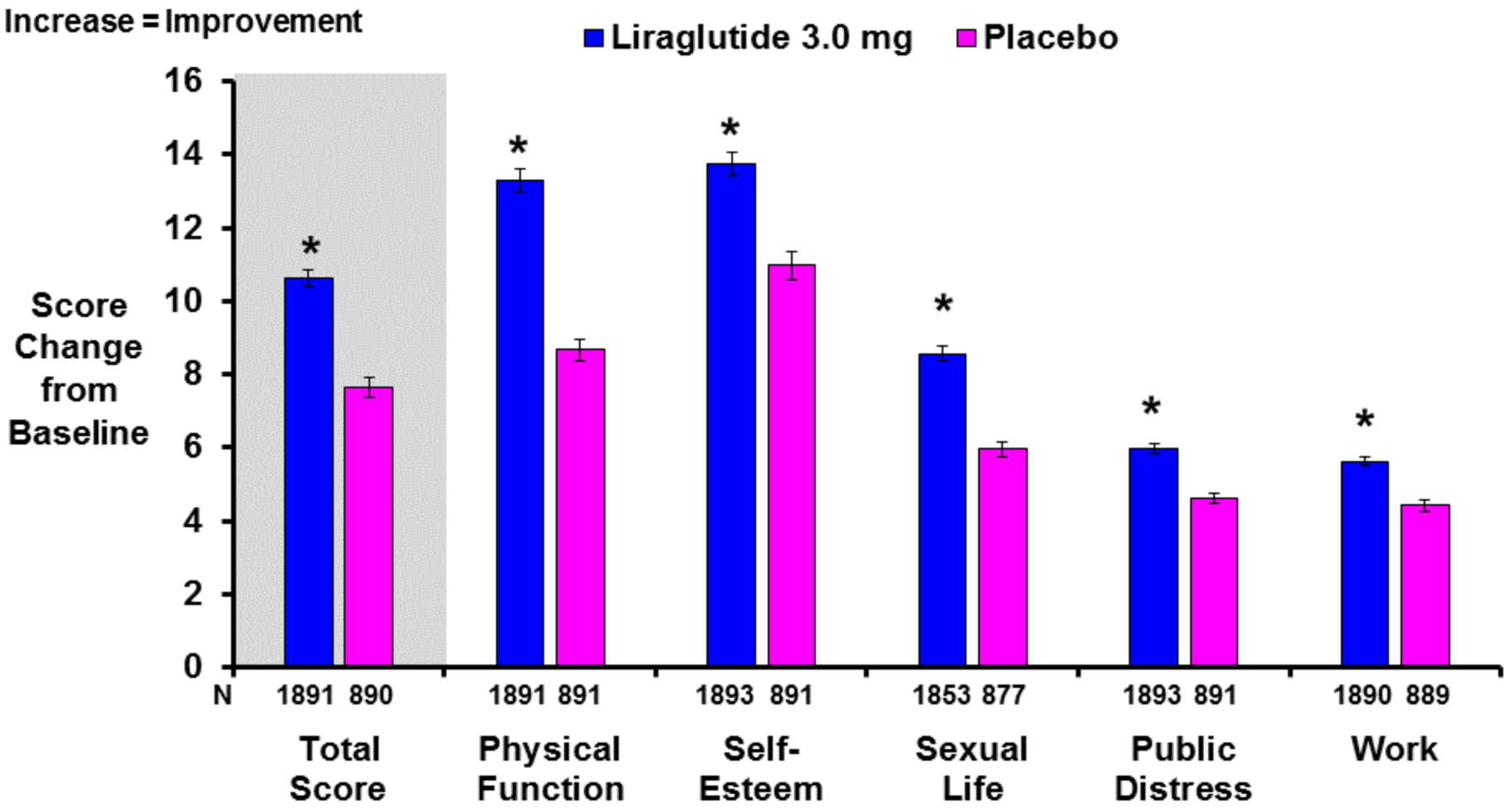
Trial 1839: Liraglutide 3.0 mg had Favorable Effects on Multiple Measures



Secondary Endpoints Address Complexities and Complications of Obesity

- Pre-diabetes/progression to T2DM diagnosis
- Glycemic parameters in patients with T2DM
- Cardiometabolic parameters
  - Waist circumference
  - Blood pressure
  - Lipids
  - Cardiovascular risk markers
- Quality of life

Trial 1839: Liraglutide 3.0 mg Significantly Improved Quality of Life, IWQoL-Lite



* *p*-value < 0.05; data are observed means +/- SE

N: Number of patients contributing to the analysis; change from baseline (FAS, LOCF)

Summary: Meaningful, Significant, Sustained Weight Loss with Liraglutide 3.0 mg

- Met all primary endpoints
- Met FDA weight loss benchmarks
  - 60% patients lost ≥ 5% weight
- Weight loss consistent across demographic sub-groups
- Weight loss maintained while on therapy
- Improvements in weight-related co-morbidities, CV risk markers, QoL

Safety of Liraglutide 3.0 mg

Alan Moses, MD

Senior Vice President

Global Chief Medical Officer

Novo Nordisk

Overview of Safety Presentation

- General safety data from weight management program
- Pre-specified adverse events of special interest

Data Sources for Safety Assessment

Liraglutide 3.0 mg Weight Management Program

1 Phase 2 Trial, 4 Phase 3 Trials

Liraglutide = 3,872 patients **Placebo = 1,941 patients**

120-Day Safety Update Data (Trial 1839 Extension)

Liraglutide in Type 2 Diabetes Mellitus Programs

24 Phase 2 and 3 Trials

Liraglutide = 7,037 patients **Placebo/Comparator = 3,677 patients**

Type 2 Diabetes Mellitus Postmarketing Surveillance Data

Patient Years of Exposure = > 3,300,000

AEs Reported by ≥ 5% Patients on Liraglutide 3.0 mg and More Commonly than Placebo

Preferred Term	Liraglutide 3.0 mg (N = 3384) %	Placebo (N = 1941) %
Total Adverse Events	91.6	83.6
Nausea	39.3	13.8
Diarrhea	20.9	9.9
Constipation	19.4	8.5
Vomiting	15.7	3.9
Headache	13.6	12.6
Decreased appetite	10.0	2.3
Dyspepsia	9.6	2.7
Fatigue	7.5	4.6
Dizziness	6.9	5.0
Abdominal pain	5.4	3.1
Lipase increased	5.3	2.2
Abdominal pain upper	5.1	2.7

NDA, weight management program (pooled phase 2 and 3 trials); N, number of patients
AEs of hypoglycemia are not included. AEs of hypoglycemia were common in patients with T2DM

SAEs Reported by ≥ 0.2% of Patients on Liraglutide 3.0 mg and More Commonly than Placebo

Preferred Term	Liraglutide 3.0 mg (N = 3384) %	Placebo (N = 1941) %
Total SAEs[1]	6.3	4.6
Cholelithiasis	0.8	0.3
Cholecystitis acute	0.4	0.0
Osteoarthritis	0.2	0.0

	Liraglutide 3.0 mg (N = 3384)	Liraglutide 1.8 mg (N = 300)	Placebo (N = 1941)
Deaths[1,2]	2	1	3

N, number of patients
1. NDA, weight management program (pooled phase 2 and 3 trials)
2. Includes data from 120-Day Safety Update (Trial 1839 Extension)

Adverse Events of Special Interest to be Discussed

- Gallbladder safety
- Pancreatic safety
- Cardiovascular safety
- Neoplasms
- Neuro-psychiatric safety

Adverse Events of Special Interest

- Gallbladder safety
- Pancreatic safety
- Cardiovascular safety
- Neoplasms
- Neuro-psychiatric safety

Gallbladder-Related Adverse Events

	Liraglutide 3.0 mg (N = 3384)		Placebo (N = 1941)	
	% of Patients	Number of Events	% of Patients	Number of Events
Adverse Events	2.3	91	0.9	20
Serious Adverse Events	1.2	48	0.3	6

- Liraglutide 3.0 mg patients experienced greater weight loss
- Gallbladder events associated with magnitude of weight loss

NDA, weight management program (pooled phase 2 and 3 trials)

Adverse Events of Special Interest

- Gallbladder safety
- Pancreatic safety
- Cardiovascular safety
- Neoplasms
- Neuro-psychiatric safety

Adverse Events of Special Interest: Pancreatitis

- All GLP-1 receptor agonists include label warning
- Adjudication criteria (2 of 3 criteria to be met)
  - Characteristic upper abdominal pain
  - Amylase/lipase elevation ≥ 3x UNL
  - Imaging consistent with pancreatic inflammation

UNL: upper normal limit

Confirmed Pancreatitis Events Across Phase 3 Trials (through 120-Day Safety Update)

	Liraglutide 3.0 mg (N = 3291)	Liraglutide 1.8 mg (N = 210)	Placebo (N = 1843)
	Number of Events		
Confirmed acute pancreatitis (%, R)	12 (0.4%, 0.26)	0	1 (<0.1%, <0.1)
Main period	7	0	1
Re-randomized period	1*	0	0
Withdrawn patients	2	0	0
120-Day Safety Update	2	0	0

*Event occurred 12 days after re-randomization to Placebo
N, number of patients; R: Event rate per 100 years of time at risk
Pancreatitis events from phase 2 trial were not sent for adjudication, pooled phase 3 trials

Confirmed Pancreatitis Events in Phase 3 Trials (through 120-Day Safety Update)

Treatment	Severity (Atlanta criteria[1])	Exposure at Onset (days)	Imaging Positive for Pancreatitis	Gallstones	
				By Imaging	↑ LFTs
Liraglutide 3.0 mg	Mild	24			
	Mild	29			
	Mild	31			✓ ALT 4x
	Mild	35[2]	✓		✓ ALT 3x
	Mild	43	✓		
	Moderately severe	170[3]	✓	✓	✓
	Mild	277			
	Moderately severe	283	✓	✓	✓ ALT 8x
	Moderately severe	330	✓		✓
	Mild	392[4]			✓ ALT 5x
	Mild	410			
	Mild	626	✓		
Placebo	Mild	287	✓	✓	✓ ALT 2.5x

1. Evaluated by Novo Nordisk; 2. After withdrawal, event onset 74 days after last dose; 3. After withdrawal, event onset 124 days after last dose; 4. Re-randomized period, event onset 12 days after last liraglutide dose. LFT: Liver Function Test

Post-Marketing Data to Evaluate Pancreatic Safety

- Prospective study in pharmacovigilance program
- Pancreatic diagnoses in large medical claims database
- Evaluating initiators of Victoza® vs. “matched” patients on other diabetes medications

No Increase in Acute Pancreatitis – Diagnoses from Medical Claims Database

Comparator	Liraglutide N	Comparator N	Liraglutide Relative Risk	95% CI
Pioglitazone	15,718	15,721	0.9	0.7, 1.2
Metformin	20,143	20,135	1.0	0.8, 1.2
Sulphonylurea*	20,588	20,596	1.0	0.8, 1.2
DPP-4 inhibitors**	17,976	17,974	1.0	0.8, 1.3
Exenatide***	7,728	7,733	0.9	0.6, 1.3

- Initiators 01 Feb 2010 to 31 Dec 2012; follow-up through 31 Mar 2013
- > 25,000 PYE liraglutide initiators; propensity score–based matching with comparators

CI, confidence interval; DPP-4, dipeptidyl peptidase-4; PYE, patient-years of exposure;
*glipizide, glyburide, glimepiride; **sitagliptin, saxagliptin, linagliptin; *** exenatide QD and QW

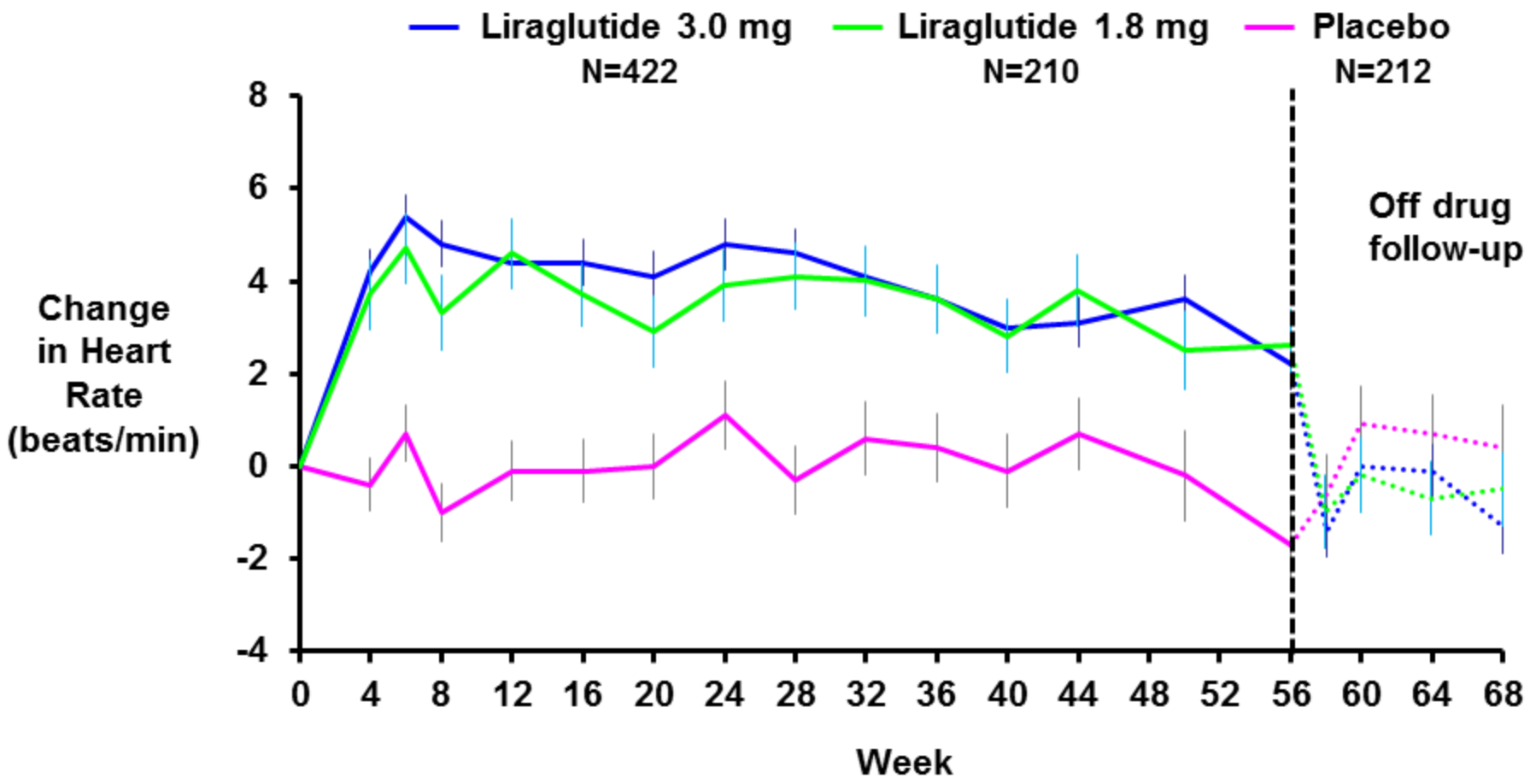
Pancreatic Safety Summary

- Nonclinical: no liraglutide induced pancreatic inflammation/pancreatitis
- Clinical studies: numerical excess; some cases associated with gallstones
- Post-marketing claims database: no excess of drug-induced pancreatitis
- Current class label guides prescribers and patients
- Additional data to be collected as part of risk management

Adverse Events of Special Interest: Cardiovascular Safety

- Gallbladder safety
- Pancreatic safety
- Cardiovascular safety
- Neoplasms
- Neuro-psychiatric safety

Similar and Reversible Effects on Heart Rate with Liraglutide 3.0 mg and 1.8 mg



NDA; N, number of patients
Trial 1922 (trial in Type 2 Diabetes Mellitus); mean +/- SE

Categorical Increases in Heart Rate

Heart Rate Increase from Baseline at ≥ 2 Consecutive Visits	Liraglutide 3.0 mg (N = 3384) % Patients	Placebo (N = 1941) % Patients
> 10 bpm increase	34.0	19.1
> 20 bpm increase	4.9	1.7

Heart Rate at ≥ 2 Consecutive Visits	Liraglutide 3.0 mg (N = 3384) % Patients	Placebo (N = 1941) % Patients
HR > 80 bpm	36.6	23.0
HR > 90 bpm	7.3	4.0

bpm, beats per minute; HR, heart rate
Baseline pulse: liraglutide 3.0 mg - 71.6 bpm and placebo - 71.3 bpm
NDA; weight management program (pooled phase 2 and 3 trials)

Cardiac Arrhythmia AEs by MedDRA Search

- No increase in overall arrhythmia adverse events
  - Liraglutide: 4.4 events/100 PYE
  - Placebo: 4.0 events/100 PYE
- AEs of "tachycardia" increased with liraglutide 3.0 mg
  - Liraglutide 3.0 mg: 0.6% of patients
  - Placebo: 0.1% of patients

NDA; weight management program (pooled phase 2 and 3 trials)

Data Show No Increased Risk for MACE - Prospectively Defined Meta-Analysis

- Time from 1st drug date to 1st Major Adverse Cardiovascular Event (MACE)
  - Cardiovascular death
  - Non-fatal myocardial infarction
  - Non-fatal stroke
- Events captured up to 30 days after last drug date
- Total liraglutide versus total comparator

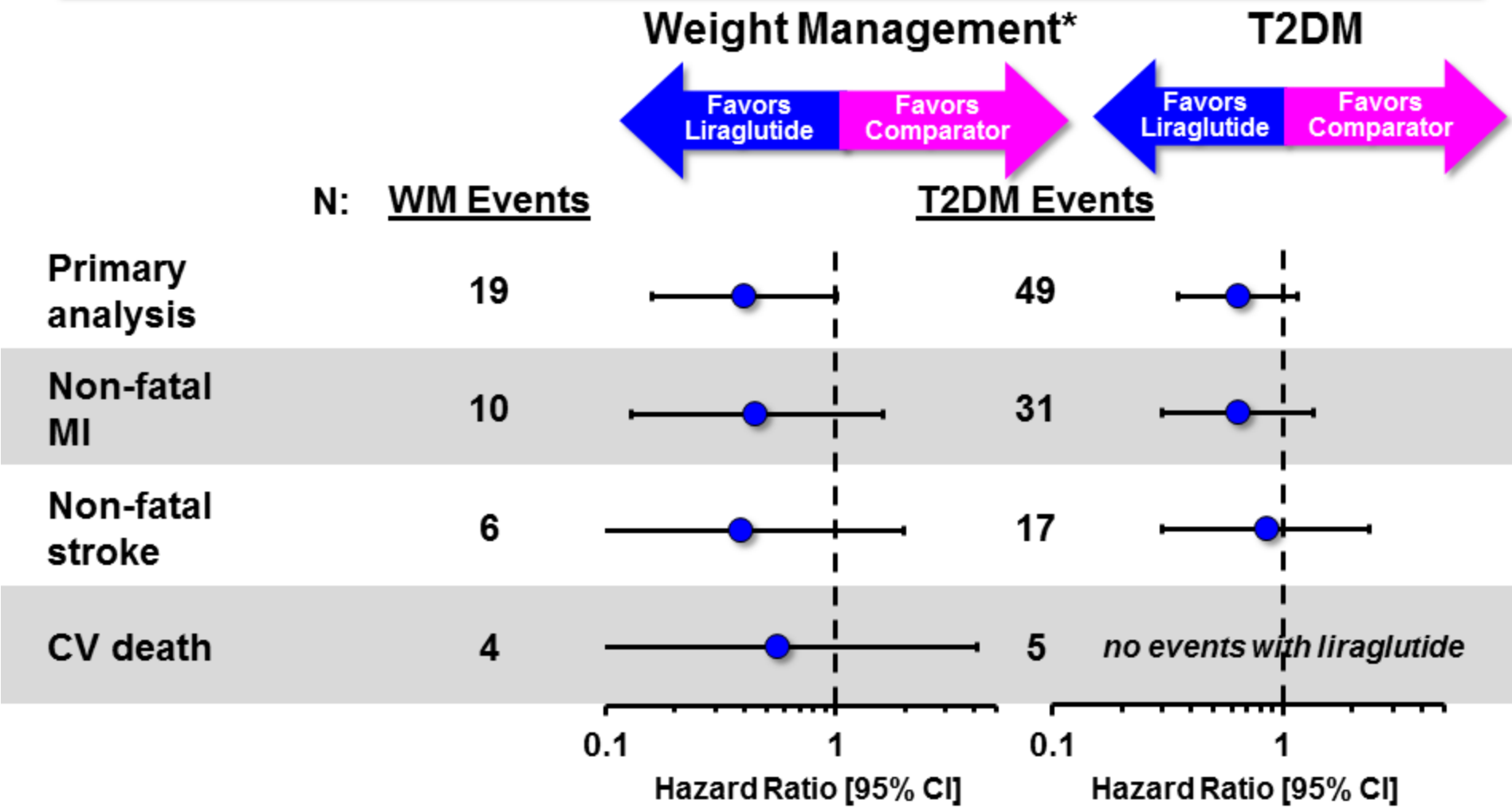
Adjudicated MACE in Weight Management Program (through 120-Day Safety Update)

	Total Liraglutide (N = 3872)			Total Comparator (N = 2036)		
	N	Events	R	N	Events	R
Confirmed events	9	10	0.20	10	10	0.41
Non-fatal myocardial infarction	5	5	0.10	5	5	0.20
Non-fatal stroke	3	3	0.06	3	3	0.12
Cardiovascular death	2	2	0.04	2	2	0.08

Hazard Ratio = 0.40 [0.16; 1.01]

N = Number of Patients; R = event rate per 100 person-years of exposure; on treatment analysis population
Patient in 1839 extension also had a non-fatal MI in main part of trial.
Weight management program (pooled phase 2 and 3 trials)

No Evidence of Increased MACE Risk in Weight Management and T2DM Programs



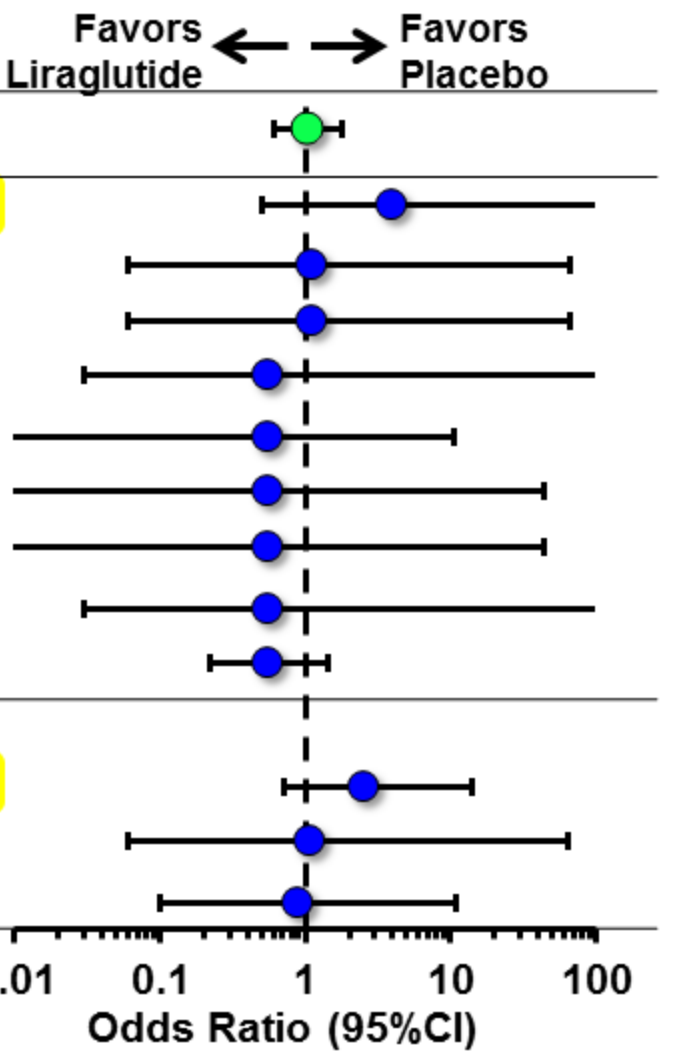
*Including 120-Day Safety Update; events are those contributing to analysis
WM, weight management; T2DM: Type 2 Diabetes Mellitus; MI, myocardial infarction; CV, cardiovascular

Adverse Events of Special Interest: Cardiovascular Safety

- Gallbladder safety
- Pancreatic safety
- Cardiovascular safety
- Neoplasms
- Neuro-psychiatric safety

Confirmed Malignant and Pre-Malignant Neoplasms: Phase 3 Trials (through 120-Day Safety Update)

	Number of Patients	
	Total Liraglutide (N = 3501)	Placebo (N = 1843)
Malignant and Pre-Malignant	**45**	**23**
Thyroid	7	1
Colorectal	2	1
Lymphomas	2	1
Pancreatic	1	0
Oral	0	1
Bladder	1	1
Liver	1	1
Laryngeal	1	0
Skin	11	11
Gender-specific tumors:		
Breast (women)	14	3
Female reproductive (women)	2	1
Male reproductive (men)	3	2



All events occurred with 3.0 mg dose
Neoplasms from phase 2 trial were not sent for adjudication

Confirmed Breast Neoplasms in Phase 2 and 3 Trials (through 120-Day Safety Update)

	Liraglutide 3.0 mg (N = 2379)			Placebo (N = 1300)		
	n	%	R	n	%	R
Time at risk, years		**3330**			**1669**	
Malignant	11	0.46	0.36	2	0.15	0.12
Pre-malignant	3	0.13	0.09	1	0.08	0.06
Benign	2	0.08	0.06	0	0	0

Two additional events in year 2, non-adjudicated Phase 2 Trial 1807

- **Breast cancer (liraglutide 1.8 mg/2.4 mg)**
- **Intra-ductal papilloma of breast (liraglutide 3.0 mg/3.0 mg), non-SAE**

N, total number of women; n, number of women with events; R, rate of events per 100 years of time at risk

Malignant Breast Neoplasms in Phase 3 Trials (through 120-Day Safety Update)

Age	Diagnosis Study Day (EAC)	Screen Detected	Grade	Stage		Receptor Status (E, P)
				EAC	Node	
Liraglutide 3.0 mg N=2379						
51	30	✓	2	Stage 3: advanced	N1	+/+
60	142/224		2	Stage 1: localized x 2	N1	+/+
43	193		3	Stage 3: advanced	N1	-/-
62	222	✓	2	Stage 2: locally advanced	N1	Unknown
47	258		1	Stage 1: localized	N1	+/+
67	313		2-3	Stage 4: recurrent	N1	-/-
55	342	✓	3	Stage 1: localized		-/-
37	373			Unknown		
57	413	✓	2	Stage 3: advanced	N1	+/+
53	545	✓	1	Stage 1: localized		+/+
58	756	✓	2	Stage 2: locally advanced	N1	+/+
Placebo N=1300						
40	282	✓	2	Stage 3: advanced	N1	+/+
62	477	Unknown	2	Stage 1: localized		+/+

EAC: Event adjudication committee; E, estrogen; P, progesterone

Pre-Malignant Breast Neoplasms in Phase 3 Trials (through 120-Day Safety Update)

Age	Diagnosis Study Day (EAC)	Screen Detected	Diagnosis Based on Source Documents	Grade	Stage (TNM)	Receptor Status (E, P)
Liraglutide 3.0 mg						
54	31	✓	Ductal carcinoma *in situ*	3	pTis Nx Mx	+/+
47	152	✓	Ductal carcinoma *in situ*	3	Tis Nx Mx	+/+
59	302	✓	Ductal carcinoma *in situ*	2	pTis Nx Mx	+/-
Placebo						
49	169	✓	Ductal carcinoma *in situ*	2	pTis Nx Mx	+/+

EAC: Event adjudication committee; E, estrogen; P, progesterone

Summary of Malignant Breast Neoplasms

- Liraglutide not mutagenic or genotoxic
- No treatment-related increase in mammary tumors in non-clinical carcinogenicity studies
- No known association between GLP-1R agonists and breast cancer risk
- 8 cases of breast cancer in T2DM clinical trials (> 3,000 PYR)
- Information to be included in label

PYR: patient years at risk

Two Types of Thyroid Neoplasms

- Medullary thyroid cancer
  - Derived from C-cells
  - Very rare in general population
- Papillary and follicular thyroid neoplasms
  - Derived from thyroid follicular cells
  - Very common in general population

Harach et al., Cancer 1985; 56: 531-538

Medullary Thyroid Carcinoma: A Focus for GLP-1 Receptor Agonists

- Rodents: Increase in thyroid C-cell hyperplasia and tumors
- Non-human primates: No C-cell hyperplasia or tumors
- Clinical Trials (> 12,000 PYE)
  - No liraglutide effect on calcitonin
  - No cases of MTC with liraglutide
    - 3 cases with comparator or placebo
- Victoza® post-marketing experience:
  - No MTC cases on liraglutide in MTC registry
  - No MTC cases on liraglutide in medical claims database
  - 12 spontaneous reports (> 3.3 million PYE)

MTC = medullary thyroid carcinoma

Low Incidence of Clinically Significant Calcitonin Concentrations

	Liraglutide 3.0 mg		Placebo	
	N	n (%)	N	n (%)
Calcitonin ≥ 20 ng/L				
Baseline	3383	15 (0.4)	1941	5 (0.3)
End of study (LOCF)	3315	16 (0.5)	1878	3 (0.2)
Increase at any visit				
From < 20 to ≥ 20 ng/L		16 (0.5)		7 (0.4)
From < 50 to ≥ 50 ng/L		1 (<0.1)		2 (0.1)
Persistent increase*				
From < 20 to ≥ 20 ng/L		1 (<0.1)		1 (0.1)
From < 50 to ≥ 50 ng/L		0		0

*All post-baseline value(s)
NDA, weight management program (pooled phase 2 and 3 trials)

Confirmed Non-MTC Thyroid Neoplasms in Phase 3 Trials (through 120-Day Safety Update)

	Liraglutide 3.0 mg (N = 3291)			Placebo (N = 1843)		
	n	%	R	n	%	R
Time at risk, years		**4529**			**2287**	
Malignant	4	0.12	0.09	0	0	0
Pre-malignant/ microcarcinomas	3	0.09	0.07	0	0	0
Benign	1	0.03	0.02	0	0	0

N, total number of patients; n, number of patients with events; R, rate of events per 100 years of time at risk

Summary of Non-MTC Malignant Thyroid Neoplasms

- No increase in non-MTC thyroid malignancies in non-clinical studies
- No GLP-1 receptors on follicular thyroid cells
- Imbalance in development programs
  - Majority of cases incidental or identified because of findings at screening
- Information to be included in label and monitored through post-marketing activities

Adverse Events of Special Interest

- Gallbladder safety
- Pancreatic safety
- Cardiovascular safety
- Neoplasms
- Neuro-psychiatric safety

Effects of Liraglutide 3.0 mg on Psychiatric Adverse Events

	Liraglutide 3.0 mg (N = 3384)		Placebo (N = 1941)	
Most Common Events	**n (%)**	**R**	**n (%)**	**R**
Any psychiatric event	366 (10.8)	15.4	197 (10.1)	15.3
Insomnia	80 (2.4)	3.0	33 (1.7)	2.1
Anxiety	68 (2.0)	2.4	31 (1.6)	2.1
Depression	62 (1.8)	2.1	31 (1.6)	2.0
Stress	19 (0.6)	0.7	16 (0.8)	1.0
Depressed mood	16 (0.5)	0.6	8 (0.4)	0.5
Events Related to Suicidal Ideation or Behavior				
Suicidal ideation*	3 (<0.1)	0.1	0	0
Suicidal attempt	1 (<0.1)	<0.1	0	0
Depressed suicidal	1 (<0.1)	<0.1	0	0

* One additional event of suicidal ideation in ongoing extension trial
Events identified by MedDRA search; R, event rate per 100 years exposure
NDA, weight management program (pooled phase 2 and 3 trials)

Liraglutide 3.0 mg Did Not Increase Depression or Suicidality Based on Validated Instruments

PHQ-9 Score	Liraglutide 3.0 mg (N = 3291)		Placebo (N = 1843)	
Baseline, mean (SD)	2.8	(3.0)	2.9	(3.1)
End of Treatment, mean (SD)	1.8	(2.6)	1.9	(2.7)
Any score ≥ 10, n (%)	199	(6.1)	124	(6.8)
Suicidality (Q9)*, n (%)	58	(1.8)	41	(2.2)
C-SSRS (post-baseline)	**n**	**%**	**n**	**%**
Suicidal Ideation	21	0.6	14	0.8
Type 4	1	<0.1	1	0.1
Type 5	0	0	1	0.1
Suicidal Behavior	1	<0.1	0	0

* "Thoughts that you would be better off dead, or of hurting yourself"
C-SSRS: Columbia Suicide Severity Rating Scale
NDA, weight management program (pooled phase 3 trials)

Safety Summary

- Well-described safety profile
- Consistent with previous development, clinical experience
- Safety profile confirmed in post-marketing
- Observations for further investigation
  - Gallbladder disease
  - Imbalanced number of breast neoplasms

Benefit Risk Summary and Risk Management Proposal

Anne Phillips, MD

Senior Vice President

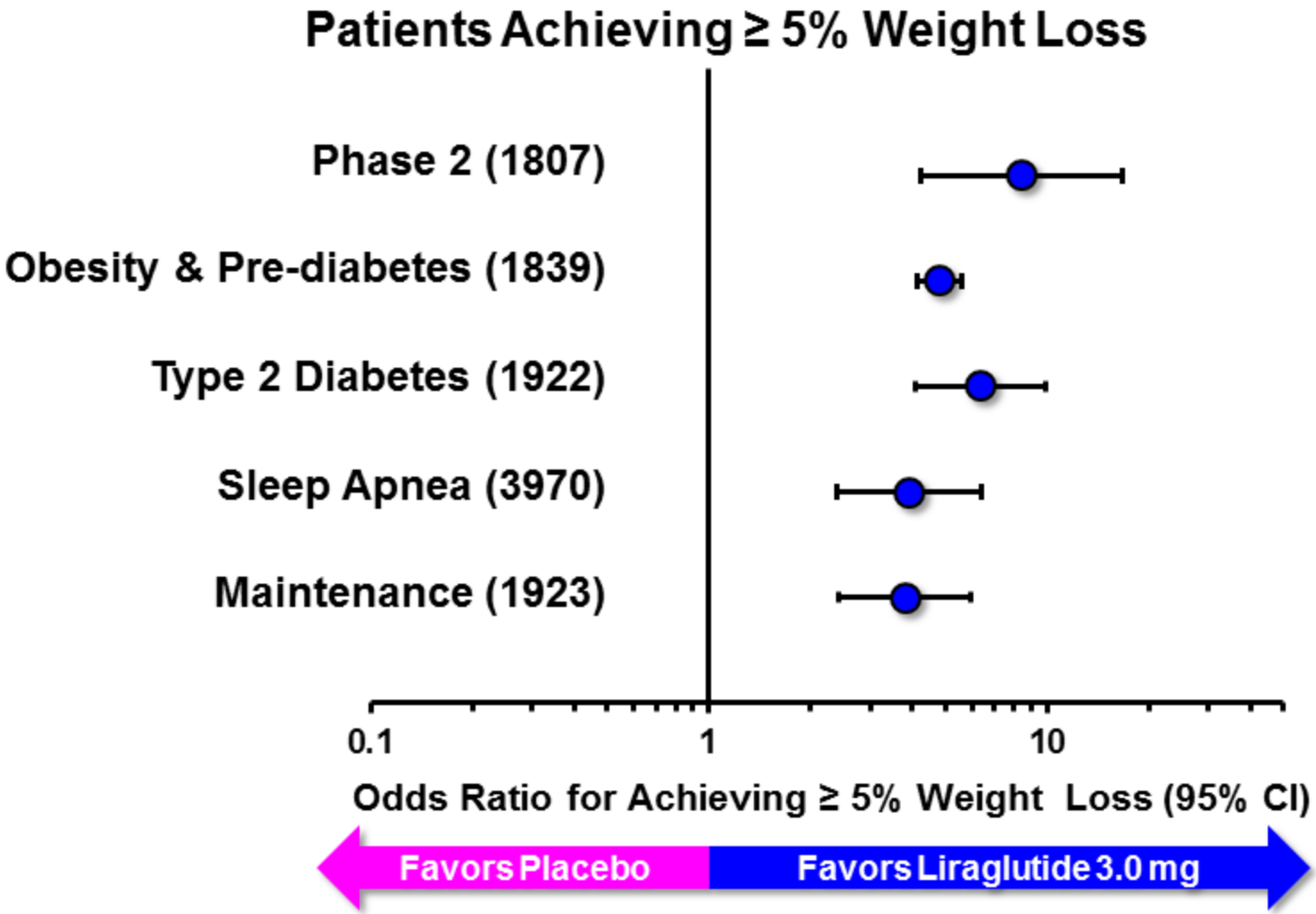
Clinical, Medical and Regulatory

Novo Nordisk

Need for New Treatment Options to Address Risks of Obesity

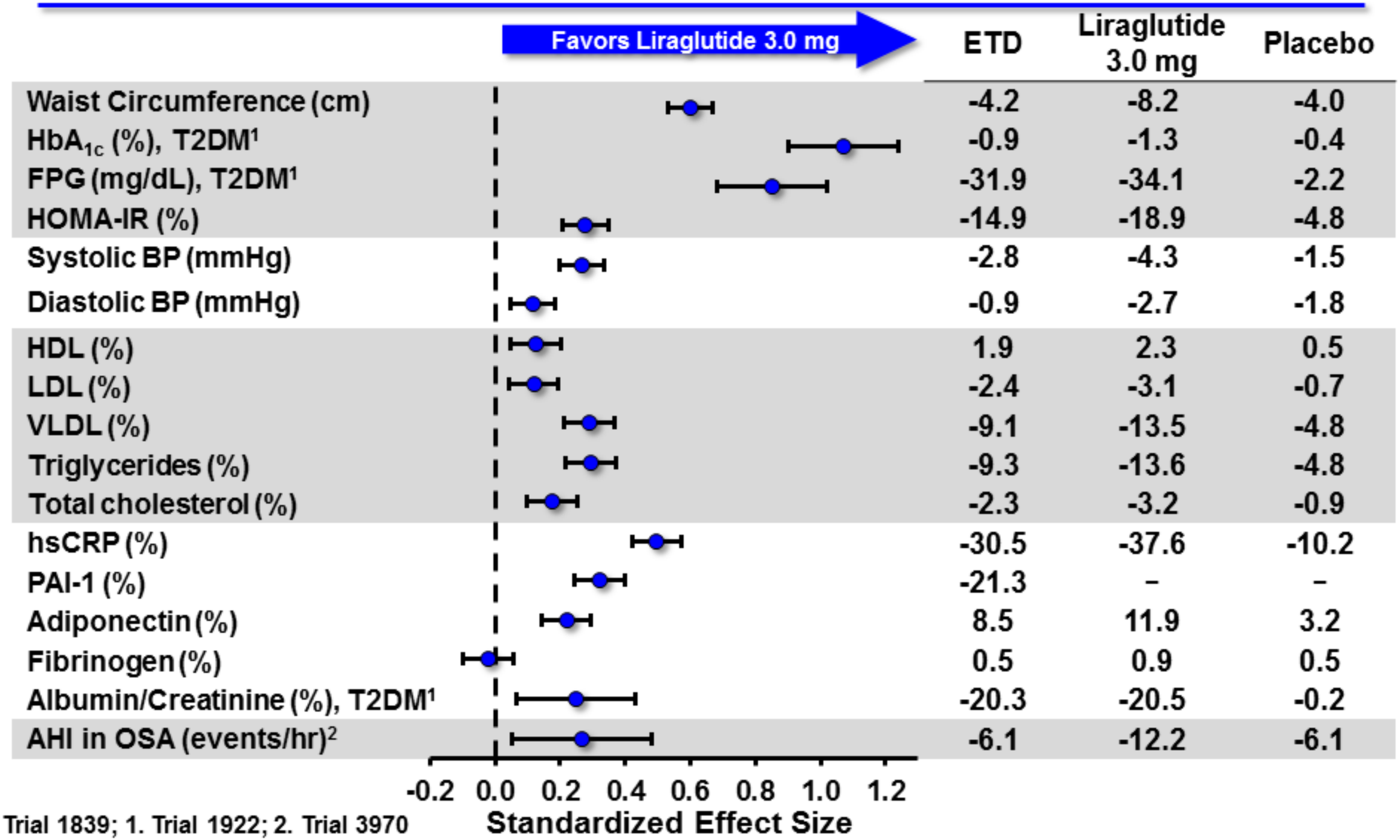
- Overweight and obese population is at serious risk
  - Type 2 diabetes, cardiovascular diseases, fatty liver disease, sleep apnea, gallbladder disease, cancer, and decreased life span
  - Depression and impaired mobility
- Greater the weight loss, greater the benefits

Liraglutide 3.0 mg Produced Significant Weight Loss in All Trials



FAS with LOCF. Estimated odds ratio.

Favorable Changes in Cardiometabolic Parameters



	ETD	Liraglutide 3.0 mg	Placebo
Waist Circumference (cm)	-4.2	-8.2	-4.0
HbA_{1c} (%), T2DM[1]	-0.9	-1.3	-0.4
FPG (mg/dL), T2DM[1]	-31.9	-34.1	-2.2
HOMA-IR (%)	-14.9	-18.9	-4.8
Systolic BP (mmHg)	-2.8	-4.3	-1.5
Diastolic BP (mmHg)	-0.9	-2.7	-1.8
HDL (%)	1.9	2.3	0.5
LDL (%)	-2.4	-3.1	-0.7
VLDL (%)	-9.1	-13.5	-4.8
Triglycerides (%)	-9.3	-13.6	-4.8
Total cholesterol (%)	-2.3	-3.2	-0.9
hsCRP (%)	-30.5	-37.6	-10.2
PAI-1 (%)	-21.3	–	–
Adiponectin (%)	8.5	11.9	3.2
Fibrinogen (%)	0.5	0.9	0.5
Albumin/Creatinine (%), T2DM[1]	-20.3	-20.5	-0.2
AHI in OSA (events/hr)[2]	-6.1	-12.2	-6.1

Trial 1839; 1. Trial 1922; 2. Trial 3970

Overall Safety Profile

- Comparable to liraglutide diabetes program and clinical experience
- Gastrointestinal most common events
- Tolerability managed with dose escalation

Risk Management Proposal for Liraglutide 3.0 mg

Ongoing Victoza® Post-Marketing Activities form Basis of Proposed Risk Management

Risk Management Activity: Victoza® for Type 2 Diabetes	Risk Addressed	Status
Non-clinical studies	Pancreatitis, MTC	Completed
Medullary thyroid carcinoma registry	MTC	Ongoing
REMS (communication plan)	Pancreatitis, MTC	Ongoing
Medical claims database study	Pancreatitis, Neoplasms	Ongoing
Cardiovascular outcome trial (LEADER®)	CV events	Ongoing

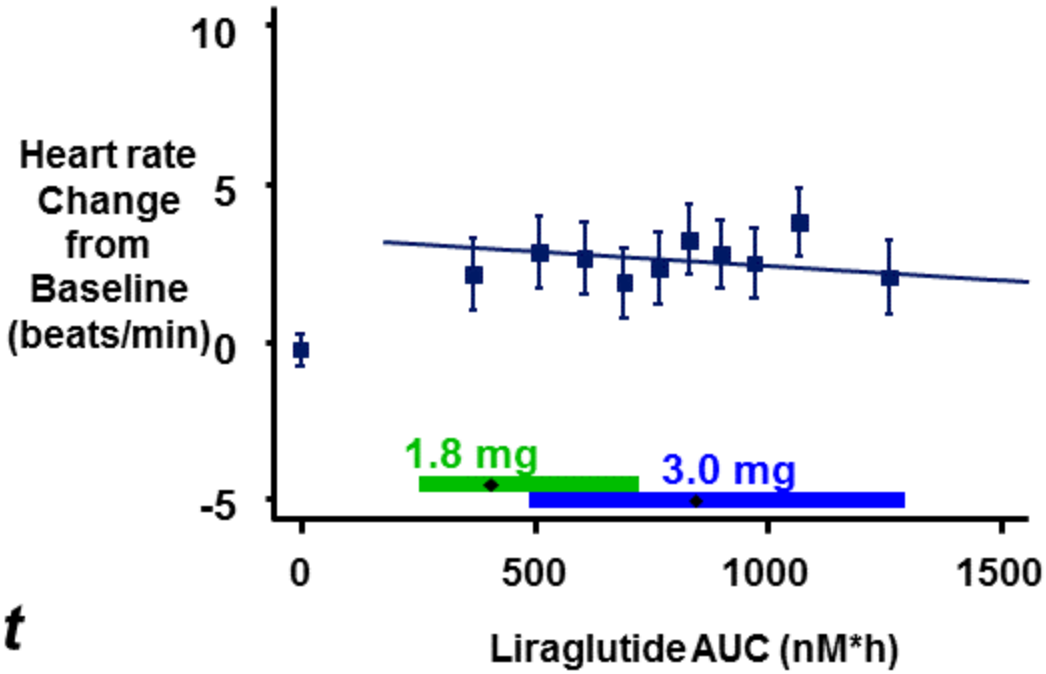
MTC, medullary thyroid carcinoma; CV, cardiovascular

LEADER®: Objectives and Design

- Primary objective: incidence of MACE in patients with T2DM taking liraglutide 1.8 mg compared with placebo, both with standard of care
  - MACE: CV death, non-fatal myocardial infarction or stroke
- Secondary objectives: include components of MACE, AEs of interest
- Two distinct populations of high risk patients
  - Prior cardiovascular disease (CVD)
  - At least one risk factor, no prior CVD
- Assumed event rate: 1.8 per 100 patient-years exposure
- 3.5 – 5 years exposure

LEADER®: CVOT Data are Relevant to Liraglutide 3.0 mg

- Appropriate patient population for weight management CVOT
- Most LEADER® patients *overweight or obese*
  - 80% BMI > 27 kg/m²
  - 59% BMI > 30 kg/m²
- All CV markers except heart rate improved with liraglutide 3.0 mg
  - Heart rate effect ***not*** dose/exposure related

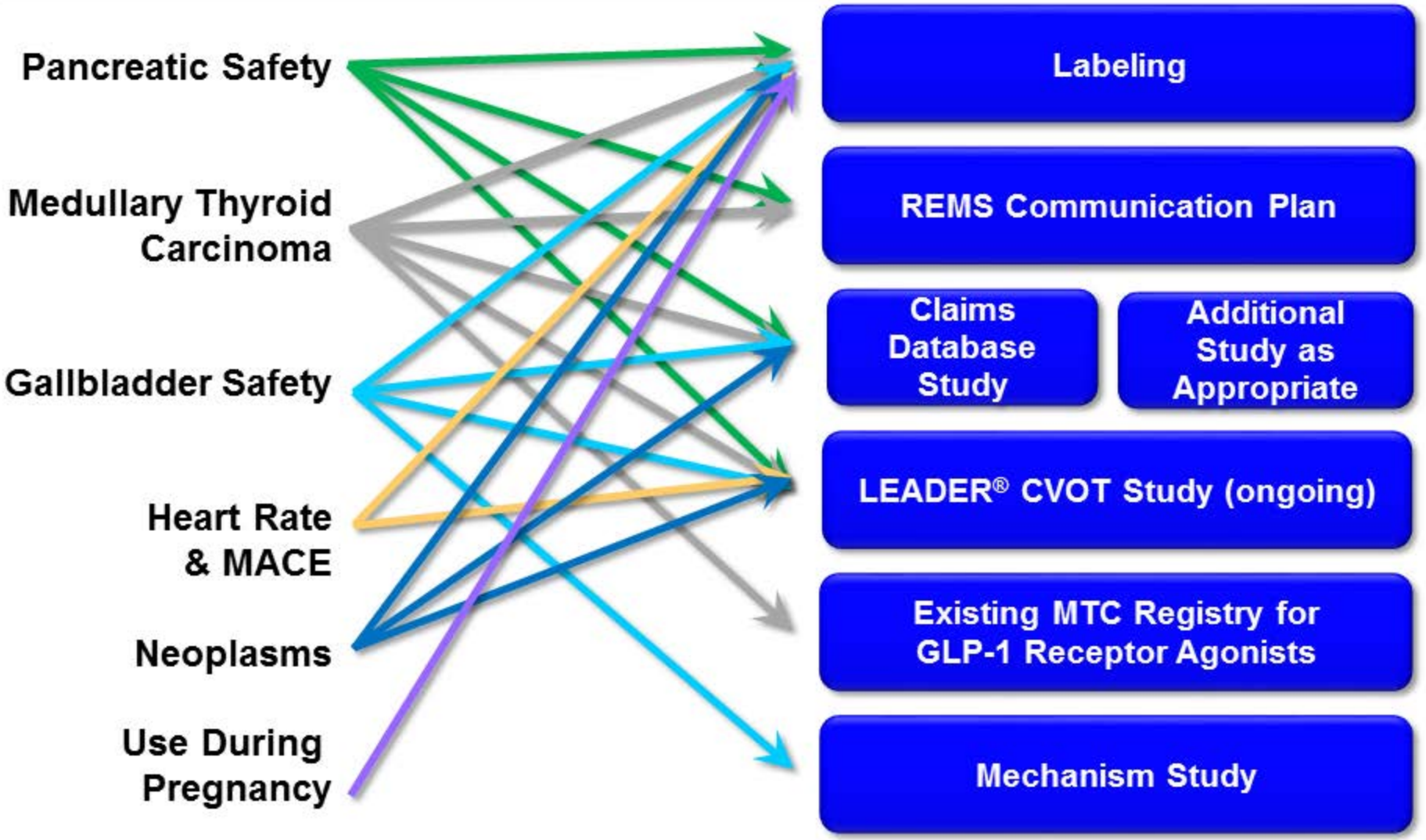


Line represents multivariate regression analysis of individual data. Heart rate change is mean (95%CI). Exposure presented as quantiles of AUC. Horizontal lines are median and 90% exposure ranges. Trials 1839, 1922, 1807.

Post-Marketing Activities for Liraglutide 3.0 mg

- Additional populations
  - Pediatric/adolescents
- Risk management objectives
  - Appropriate patient selection
  - Patient and HCP awareness
  - Better understanding of observations with uncertain relevance to liraglutide

Risk Management Plan for Liraglutide 3.0 mg



Favorable Overall Benefit-Risk Profile

- Met FDA efficacy benchmarks
- 90% of patients lost weight and most maintained weight loss
- Benefits beyond weight loss
- Well-described safety profile
- Safety consistent with previous development, clinical experience
- Comprehensive Risk Management and REMS program

Liraglutide 3.0 mg
Treatment for Weight Management

FDA Advisory Committee Presentation

September 11, 2014

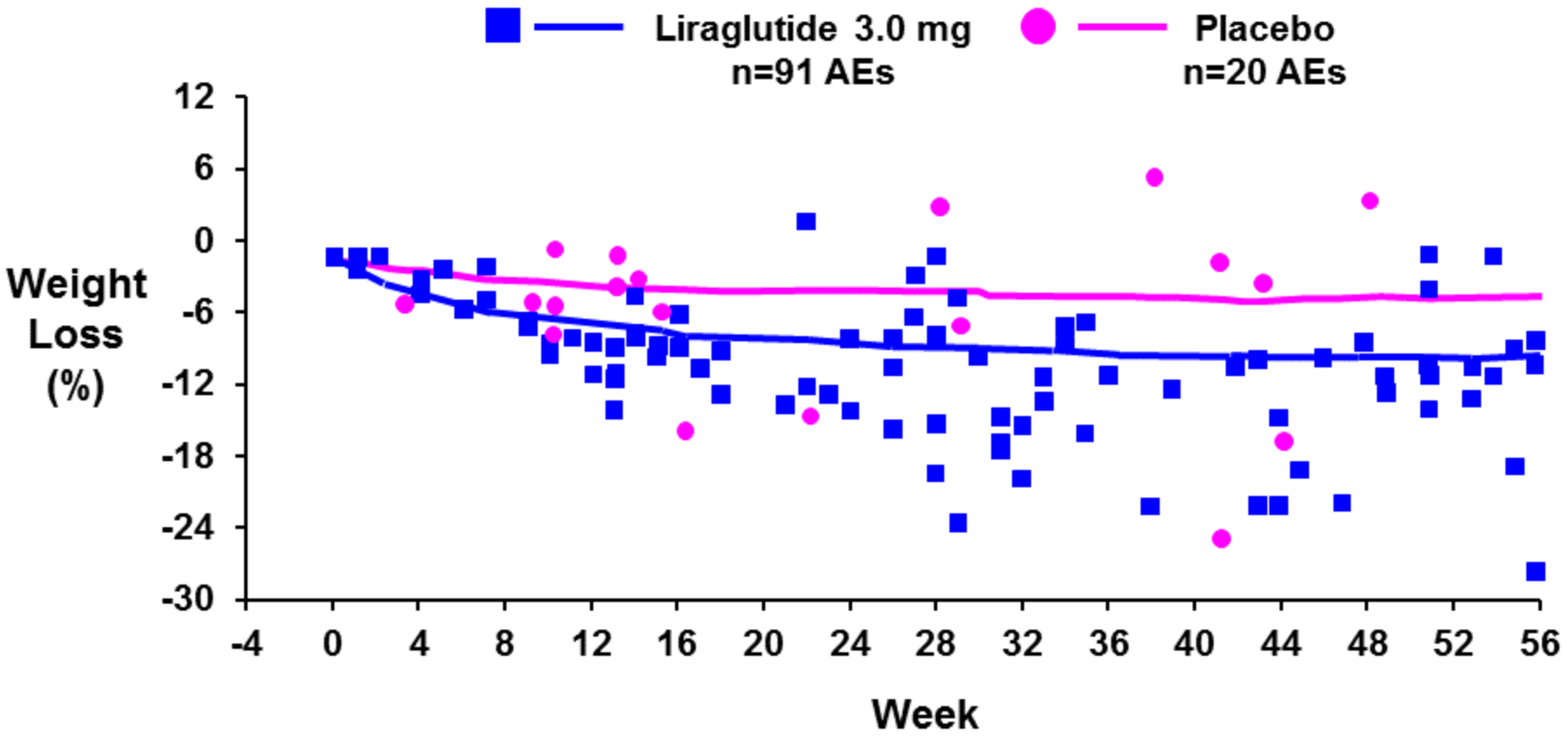
Backup Slides Shown

Pregnancies in Weight Management Program – All Periods Including 120 DSU

	Total Liraglutide		Placebo	
	N	%	N	%
Women in analysis set	2379		1300	
Pregnancies (% of women)	39	1.6*	20	1.5
Outcomes of pregnancies				
Healthy children	18	46.2	7	35.0
Spontaneous abortion	10	25.6	2	10.0
Abortion**	1	2.6	0	0
Elective abortion	4	10.3	3	15.0
Ectopic pregnancy	1	2.6	3	15.0
Lost to follow-up	1	2.6	3	15.0
Ongoing	4	10.3	2	10.0

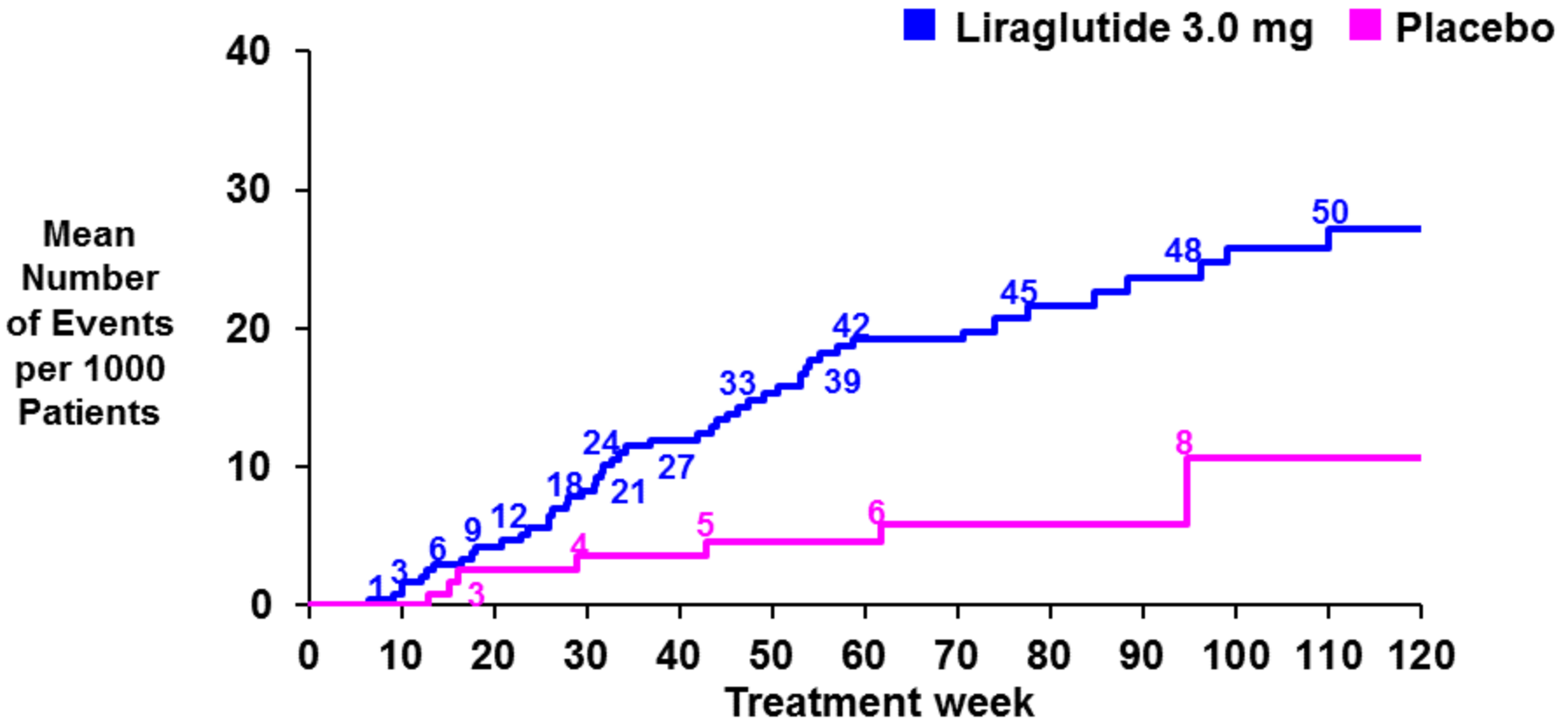
120 DSU; SAS; Novo Nordisk safety data base (cut-off 14 March 2014); All phase 2 and 3 trials incl. ongoing 1839-extension.
* one pregnancy (outcome: miscarriage) occurring in a partner of a male patient is not included; **unknown if spontaneous or induced. 120 DSU, 120 day safety update; N, number of cases.

Gallbladder-related AEs by Weight Loss at Onset of Event - NDA



NDA; SAS; Weight management pool; Treatment emergent adverse events. Graphed lines, mean weight change in weight management pool. AE, adverse event; n, number of patients with gallbladder-related AEs

Gallbladder-related SAEs: Mean Cumulative Number of Events over Time - Trial 1839 (Through 120-Day Safety Update)

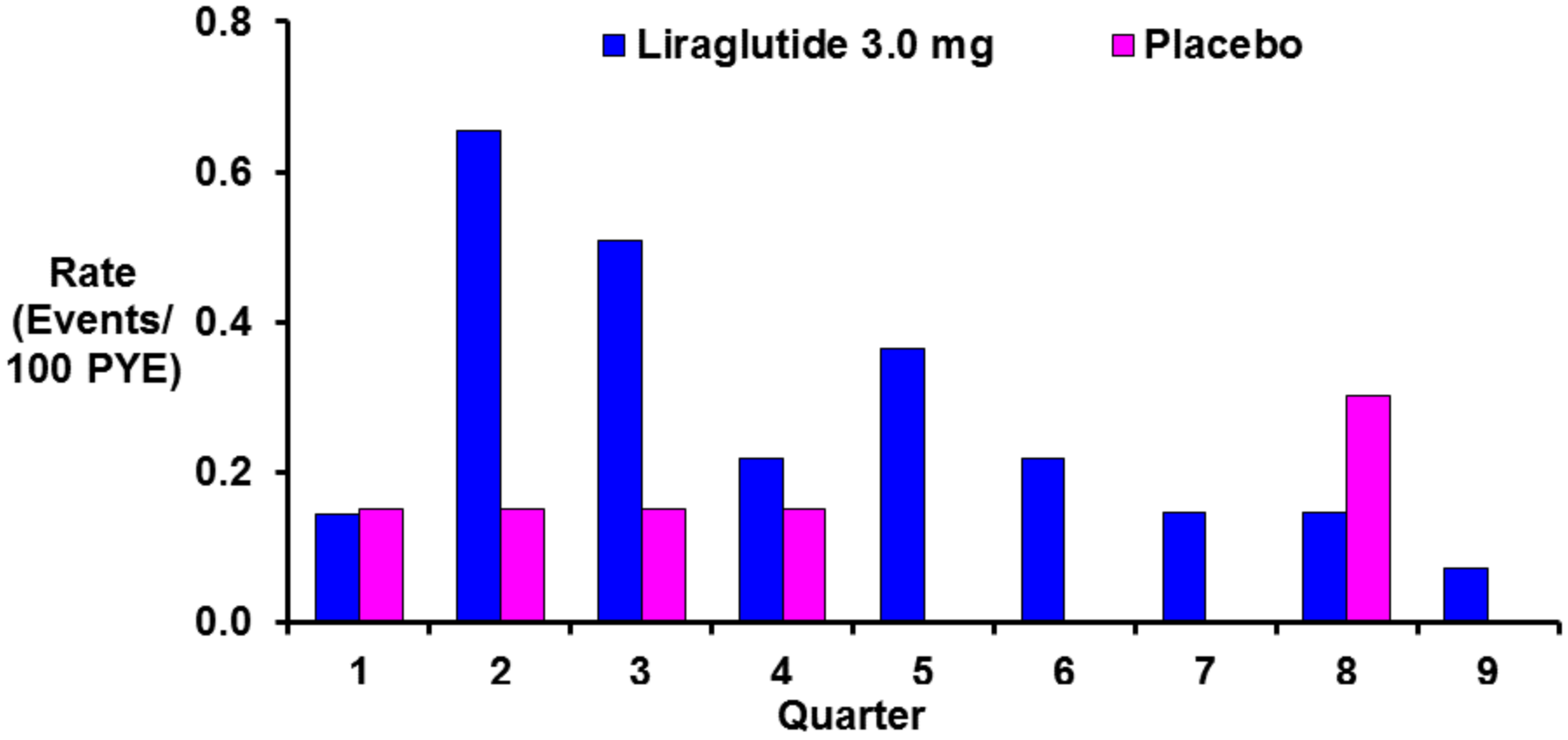


N at Risk:

Liraglutide	2378	2279	2200	2128	2086	1865	1750	1020	967	924	773	392
Placebo	1190	1113	1042	1002	968	833	768	456	425	402	327	170

NDA; SAS; Trial 1839; Treatment-emergent and non-treatment emergent events. Risk time is defined as the time between first drug date and last contact and non-treatment emergent events are included. Numbers in plot represent cumulative events at that time point. SAE, serious adverse event; TE, treatment emergent; N, number of patients at risk

Gallbladder-related SAEs: Rates by Quarter in Patients with Pre-diabetes - Trial 1839 (Through 120-Day Safety Update)



Liraglutide (n)	2	8	7	3	3	3	2	2	1
Placebo (n)	1	1	1	1	0	0	0	1	0

NDA; SAS; Trial 1839. SAE, serious adverse event; TE, treatment emergent; n, number of patients with gallbladder related SAEs; R, rate of events per 100 patient years of exposure (PYE)

Malignant Breast Neoplasms in Medical Claims Database (Optum), T2DM

	E	PYE	Liraglutide Rel. Risk	95% CI
Liraglutide	**48**	**13,563**		
All Comparators	**575**	**179,444**	**1.00**	**0.74, 1.43**
Pioglitazone	57	14,898	1.02	0.68, 1.52
Metformin	324	111,450	1.00	0.73, 1.38
Sulphonylurea*	89	27,998	1.09	0.74, 1.59
DPP-4 inhibitors**	79	17,540	0.90	0.62, 1.32
Exenatide***	26	7,557	1.08	0.67, 1.75

*glipizide, glyburide, glimepiride ; ** sitagliptin, saxagliptin, linagliptin; *** exenatide QD and QW

Optum report dated June 2014. Initiation Period: February 1, 2010 - December 31, 2012. Follow-Up Through March 31, 2013
CI, confidence interval; DPP-4, dipeptidyl peptidase-4; E, number of events; PYE, patient years of exposure; T2DM, type 2 diabetes mellitus